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SAFE CONDUCT OF THE PATIENT THROUGH CARDIAC SURGERY*

With Special Reference to Diseases of the Mitral and Aortic Valves

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AFTER decades of sporadic though brilliant attempts at cardiac surgery intense activity in this field in the past eight years has resulted in a vast new area of surgical accomplishment. These advances could only have been made against the background of knowledge of anesthesia and respiratory physiology gained during the development of thoracic surgery since the early 1930's. In similar fashion the early efforts in the cardiac field were directed toward devising technics for safe operation within the cardiac chambers and the elucidation of the physiologic principles necessary for survival during the immediate operative period. It is not presumed that the last technical advance has, in any sense of the word, been made in this rapidly expanding field. However, in the correction of mitral and pulmonic stenosis and perhaps also in aortic stenosis, mitral insufficiency and defects of the atrial septum the technics have become sufficiently stabilized to demand corresponding attention to care of the patient before and after operation. Herein lies the opportunity for improvement in mortality and rehabilitation rates.

The principles presented here are based on extensive experience with patients undergoing cardiac surgery over the past seven years. Valvuloplasty for the correction of mitral stenosis has been the commonest procedure, and our comments are pertinent to this operation in particular. However, the care of patients undergoing other types of intracardiac surgery is also considered. The diagnosis and selection of patients is not within the province of this presentation, which is concerned only with the management of the properly selected patient. It should be emphasized that this must be a team project shared by the surgeon with the cardiologist and anesthesiologist, each of whom will be called on to make important contributions.

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PREOPERATIVE PREPARATION

Digitalis

The goal in the immediate preoperative period is to bring the patient into the best possible state of cardiac compensation. If congestive heart failure or atrial fibrillation has occurred he will undoubtedly be receiving digitalis; the proper regulation of this medication is of first importance. In our experience over-digitalization has been far more common than insufficient dosage, particularly when one of the refined and potent forms of digitalis (predominantly digitoxin) has been employed, for with these agents the warning symptoms of gastrointestinal disturbance that characterize digitalis-leaf toxicity may be absent. In their place, direct myocardial toxicity is the first evidence of overdosage with the purified preparations and is manifested by ventricular extrasystoles, impaired atrioventricular conduction or alterations in the pacemaker. These warnings of myocardial irritability must be heeded if the surgeon wishes to avoid dangerous arrhythmia at the time of operation. When overdosage is present digitalis should be omitted until the signs of toxicity disappear and then resumed at a lower dosage level. In addition, since hypokalemia potentiates the toxic properties of digitalis, the administration of potassium chloride in doses of approximately 3.0 gm. a day is indicated in this situation[1] even though the serum level is within normal limits. The balance studies[2] discussed below have demonstrated a consistent depletion of body stores of potassium in patients with congestive heart failure who have undergone repeated diureses. The supplemental potassium, however, must be withheld the day before operation so that the patient does not face the usual postoperative oliguria with an excess of potassium.

It is usually best to maintain the patient with the form of digitalis that he has been receiving. The dose is regulated so that the apical rate is consistently in the range of 80 to 90 per minute. Furthermore, it has been our custom to digitalize all patients who are

to undergo a valvuloplasty even though it has not previously been required and normal sinus rhythm is present; if atrial fibrillation occurs after operation its control can be more rapidly effected when there is a basic state of digitalization. In addition the direct cardiotonic effect of this drug may protect against congestive heart failure during the period when the left ventricle is becoming adjusted to the increased volume of blood that it is called on to pump after a satisfactory opening of the stenotic mitral valve. These same considerations apply to patients about to undergo pericardiectomy and operations for mitral insufficiency and those on the aortic valve, but probably not to patients subjected to great-vessel surgery such as the shunt operations for tetralogy of Fallot, interruption of the patent ductus arteriosus and excision of a coarctation of the aorta (unless there is evidence of congestive heart failure).

Quinidine and Procaine Amide

The routine prophylactic use of quinidine or procaine (either the amide or the hydrochloride) before or during operation is contraindicated because of the obvious undesirability of depressing the myocardium. Hearts depressed by such drugs go into arrest more frequently. If irritability appears and persists during operation, these agents can always be given into a vein or directly into the heart, as discussed below.

Electrolyte Balance

The balance studies of Wilson et al.[2] have clarified many of the problems of electrolyte balance encountered in patients with mitral stenosis before and after surgery. These authors have identified two fundamental types of electrolyte pattern preoperatively in the cardiac patient. The majority of patients studied had normal or high stores of sodium in the body, as demonstrated by isotope dilution and total balance technics and serum sodium values in the normal range. In addition the total body water was almost invariably increased.

A few patients — generally those who have been in severe congestive heart failure requiring prolonged sodium restriction and vigorous mercurial diuresis — constitute the other group manifesting an actual depletion of sodium stores. The implications of these two patterns in the postoperative electrolyte response are detailed below. Only rarely have low serum sodium values been encountered preoperatively, and then only in the desperately ill patients.

Before these detailed studies were available the finding of a preoperative serum sodium value in the range of 118 to 125 milliequiv. per liter was interpreted as a sign of impending death. Indeed, such patients almost invariably died within a week despite the most careful medical management.

The preoperative finding of hyponatremia continues to be regarded as a particularly ominous sign. However, since the balance studies have become available, progressive preoperative hyponatremia has been reversed in a few cases, and some patients have been brought to and through the successful correction of their valvular lesions.

The management of this electrolyte problem consists of continued salt restriction, limitation of fluid to 1000 to 1500 cc. a day to avoid serum dilution (as discussed below) and daily weighing of the patient — a most important step. The urinary sodium concentration should also be measured. If it is elevated to more than 30 milliequiv. per liter an unregulated salt loss through the kidneys exists. This is a rare situation but one demanding special steps in treatment. Details of this management are presented by Moore.[3] If the urinary sodium, however, is below 25 milliequiv. per liter, with a low serum sodium (and in the absence of intravenous sodium infusion during collection of the specimen), conservation by the renal tubules may be considered normal.

In the vast majority of patients showing preoperative hyponatremia attempts to correct the situation by oral or intravenous infusion of saline solution have been futile. In most of these cases, in fact, high total exchangeable sodium values have been found. It is obviously undesirable to load the circulation further, thereby aggravating the congestive heart failure that is almost always present. In the presence of peripheral edema a high total exchangeable sodium has invariably been found; in these cases the administration of sodium is specifically contraindicated.

Ideally, the total exchangeable sodium should be measured to elucidate these problems, but this is rarely possible in practice. However, some general rules of thumb can be applied. Thus, if the patient with hyponatremia preoperatively has not responded to the regimen discussed above despite fluid restriction, if he is not gaining weight, if renal salt conservation is normal and if there is a possibility of sodium depletion because of vigorous salt restriction and diuresis a *single test dose* of 250 cc. of 3 per cent sodium chloride should be given. The body weight and serum sodium concentration are followed closely for seventy-two hours. If the concentration rises and he does not gain weight or form new edema a true sodium deficiency may have been present. Under such circumstances a few days of oral sodium supplementation with continued fluid restriction may produce further improvement. Any repetition of such an intravenous dose preoperatively, however, is dangerous.

In general, it is preferable to delay operation until the serum sodium level reaches 130 milliequiv. per liter or above. It should be noted that the administration of cortisone in this situation has not been found effective.

As a corollary to the above discussion it appears that the routine administration of saline solution to all patients about to undergo cardiac surgery, as recently advocated[4,5] to avoid postoperative hyponatremia, is unwise. Indeed, it may be disastrous in

the patient with Group 4 cardiac disease[6] whose circulatory balance verges on complete disintegration.

Diuretics

In the preparation of the cardiac patient for operation the judicious use of diuresis is of utmost importance. The patient should be brought down to a minimum weight, with the smallest possible amount of excess fluid, at a time when the body with its deranged circulatory apparatus faces the acute stresses of the operative procedure. Even patients with no obvious edema are given a dose of 1 cc. of Mercuhydrin early in the preoperative period. The studies of Wilson and his associates[2] have repeatedly demonstrated a high total body water even in the absence of gross edema; furthermore, the diuretic response of many nonedematous cardiac patients justifies this step. Because the diuresis often leaves the patient fatigued on the following day, the diuretic should be given at least forty-eight hours before operation.

In choosing the diuretic program, one should determine how often the patient has required such agents before hospitalization, in what dose and by which agent. A history of untoward reactions to Mercuhydrin may dictate the use of another agent (such as Thiomerin or Salyrgan). Generally speaking, however, the alleged intolerance is not confirmed, although a test dose is proper. The patient who has had ill effects in the past does not necessarily have them again under conditions of rest, digitalis regulation and chloride manipulation.

If the patient has a marked response to the first dose of the mercurial diuretic it should be repeated at intervals of forty-eight to seventy-two hours until the "optimal dry weight" has been reached. Several conditions may explain a lack of response to 1 cc. of Mercuhydrin: the patient may be in a satisfactory state of compensation and not have occult edema; the serum chlorides may be low, necessitating ammonium chloride in doses of 6 to 8 gm. a day for several days before the mercurial diuretic is repeated or a 2-cc. dose may be indicated. In a certain number of patients, chiefly those in the Group 4 classification of mitral stenosis (the preterminal)[6] and in those with constrictive pericarditis, edema, ascites and hepatomegaly may persist despite all the measures outlined above. In such cases when one is satisfied that the end point in weight reduction has been reached, the operation will have to be undertaken in a compromise state of compensation. Indeed, the presence of refractory congestive heart failure is the principal criterion for classifying a case in Group 4.

Lusk et al.[7] have demonstrated an increase in sodium excretion in normal subjects after oral saline ingestion when the legs were compressed with elastic stockings. It may be that elastic stockings will augment mercurial diuresis. Furthermore, such stockings are routinely used to prevent stagnation in the deep venous system. Potentiation of diuresis may also be obtained by the administration of aminophylline (0.25 to 0.5 gm.) by vein half an hour after the mercurial diuretic.

Low-Salt Diet

Most patients who have had evidence of congestive heart failure will have been placed on a low-salt diet (200 mg. of sodium) at some time before hospital admission, but if this has not been done, it obviously should be instituted as an adjunct to the measures discussed above in the preoperative period, with the sole exception previously mentioned.

Liver Damage

The frequency of congestive hepatomegaly and marked fatty infiltration of the liver in patients with Group 4 disease who have come to autopsy has been impressive. This observation, together with the frequent finding of jaundice and increased serum bilirubin before and after operation in patients with irreversible congestive heart failure, suggests that measures should be undertaken to improve the condition of the liver so far as possible. For this reason, in patients who have definite enlargement of the liver, operation has been delayed for at least a week or ten days for rest and preparation. The liver profile of bilirubin, total protein and albumin-globulin ratio, prothrombin time and thymol turbidity is obtained to document the clinical impression of a liver disturbance. These patients are placed on a high-carbohydrate, low-fat diet, with vitamin B supplements in addition to choline, methionine, inositol and folic acid. Granted that this is empirical polypharmacy, the clinical impression is that this period of preparation has significantly reduced the liver complications in the postoperative period. Such steps are particularly important in patients with long-standing constrictive pericarditis as well as for those with chronic congestive heart failure of other etiology.

Obviously, a patient who has been on long-term Dicumarol therapy for arterial embolism should be taken off the drug and the prothrombin time allowed to return to normal before any operative procedure is contemplated. Vitamin K is administered for any abnormally prolonged prothrombin time not traceable to anticoagulant therapy.

Antibiotics

Forty-eight hours before operation parenteral injection of penicillin is begun. This is supplemented by aerosol penicillin and streptomycin in patients with mitral stenosis in whom chronic pulmonary suppuration is present.

Hematocrit

In congenital cyanotic heart disease with increased hematocrit experience has shown that the preoperative dehydration the night before the procedure is to

be avoided because of the danger of cerebral thrombosis. This should be taken into account when one is writing the preoperative orders for such patients. Evidence is accumulating[8] that the optimal balance between oxygen transport and blood viscosity is found when the hematocrit is below 80 per cent for infants, 70 per cent for children and 60 per cent for young adults. Phlebotomy may therefore be considered if the hematocrit exceeds these values, particularly if the patient is having cerebral symptoms that may be premonitory of a cerebral thrombosis.

Rheumatic Activity

In general, whenever there is evidence of significant valvular obstruction, its relief is indicated despite the suspicion of active rheumatic carditis. Sedimentation rates, antistreptolysin titers and low-grade febrile courses have all proved to be unreliable indexes of rheumatic activity. Dramatic improvement almost invariably follows the relief of significant mitral stenosis even in cases in which the evidence is very suggestive of active carditis. In addition the rheumatic process may well be benefited by valvuloplasty since the recurring cycle of pulmonary edema and infection is broken. In more than 700 cardiac operations in patients with rheumatic heart disease there have been only 3 overt cases of reactivation of rheumatic carditis in the immediate postoperative period. Furthermore, in the same number of patients, few have experienced subsequent significant attacks of acute rheumatic fever.

In 1 dramatic case prolonged cortisone therapy converted a patient who seemed hopelessly ill into a reasonable risk, allowing a successful valvuloplasty to be performed, with eventual complete rehabilitation. However, in general, such therapy has been quite disappointing.

Subacute Bacterial Endocarditis

The question of subacute bacterial endocarditis is often raised in patients with mitral stenosis combined with a low-grade fever, but only on rare occasions has the diagnosis been proved. A significant number of patients with subacute bacterial endocarditis have undergone successful, uncomplicated valvuloplasty within several weeks of control of the blood-stream infection. In a particularly remarkable case a valvuloplasty was performed during an episode of subacute bacterial endocarditis that became apparent only when the preoperative blood cultures grew out organisms during the postoperative period. The usual routine prophylactic antibiotics apparently controlled and later sterilized the infection in this case and there were no complications. Although operation would not knowingly be undertaken in the face of such an infection the mere existence of a low-grade fever preoperatively should not delay surgical correction in the patient obviously needing it. Most of these fevers disappear after the stenosis is relieved and are presumed to be due to a low-grade pulmonary infection kept alive by the coexistence of subclinical pulmonary edema.

Hyperthyroidism

The third condition (with rheumatic activity and subacute bacterial endocarditis) in the triad of complications of mitral stenosis, often suspected preoperatively but seldom proved, is hyperthyroidism. Many patients in congestive heart failure have intolerance to heat, weight loss, anxiety, tachycardia and excessive sweating. Only in extremely rare cases have we found unequivocal hyperthyroidism. If present, it should obviously be treated, but its coexistence with obvious valvular disease has been rare indeed in this series.

Operative Management

The general mental attitude of patients facing a cardiac operation cannot be overemphasized. They should approach the procedure with confidence and expectation of success. This is best accomplished by kindness and warmth on the part of the physicians and nurses in attendance. In addition the patient's apprehensions are often allayed if he talks with others who are convalescing from a successful operation.

Tachycardia

A consistent plan of procedure on the day of operation is of utmost importance in the successful handling of a patient with mitral stenosis. Tachycardia must be avoided; it is particularly damaging to the patient with obstruction of the mitral valve in at least three ways: the precarious cardiac output may be further compromised when ventricular filling time in diastole is shortened; increased pulse rate accentuates the volume per minute of any regurgitation that may exist; and, finally, the tendency to or extent of pulmonary edema is increased as the competent right ventricle augments the volume of blood in the lungs. This vicious circle is completed by the resulting anoxia, which leads to peripheral vasodilatation and further depresses the blood pressure. For these reasons excitement is kept at a minimum, sedation is given in ample dosage, and atropine and scopolamine, which block vagal effects, are avoided.

Anesthesia

Anesthesia for any cardiac patient, but for the patient with mitral stenosis in particular, demands the utmost skill and a thorough understanding of the physiologic, pathologic and pharmacologic factors involved. Nothing can be more damaging to the cardiac patient than a rough induction. Pentothal (100 to 200 mg.) is given intravenously followed by nitrous oxide, oxygen and ether, with curare for intubation. *It is vital that a minimum of anesthetic agent be used;* there has been ample evidence that cardiac arrest

in diastole results when more than minimal amounts are given. A total volume of 15 to 30 cc. of ether is almost never exceeded during the hour to hour and a half of operation. On such a regimen the patient responds as the skin stitches are placed. The use of cyclopropane has been discontinued because of its tendency to increase cardiac irritability.

No feature of the anesthetic management of the cardiac patient is more important than ventilation, not only to afford maximal oxygenation of the myocardium but also to avoid hypercapnia, with its attendant potentiation of ventricular irritability. Recent studies indicate that this can be achieved most reliably by the use of the mechanical assistor developed by Maloney, Derrick and Whittenberger.[9] This, in essence, consists of a demand valve that gives supplemental inspiratory pressure when cycled by the patient; it allows complete emptying of the lung at atmospheric pressure in expiration. In addition, just before the intracardiac maneuver, the lung is re-expanded, and a period of hyperventilation allowed.

If the patient's cardiac rate (determined by the electrocardiogram) is still elevated after the excitement phase of induction has passed, an intravenous injection of prostigmine in doses of 0.25 mg. is given. Slowing is generally obtained by potentiation of the decelerating action of the vagus. This agent should be repeated if no effect is noted within ten minutes.

Hypotension

The second major problem facing the anesthetist and surgeon during a cardiac operation is hypotension. The peripheral vasodilatation incident to general anesthesia may cause severe hypotension or even the complete disappearance of detectable peripheral blood pressure. This may be the result of a low fixed output in valvular heart disease or constrictive pericarditis, or of myocardial inadequacy in other conditions. This undoubtedly contributes to tissue anoxia, and a serious and irreversible series of events may be initiated. In operations for, or in the presence of, coronary-artery disease hypotension may allow thrombosis to occur in partially occluded vessels. In patients with right-to-left shunts the fall in peripheral resistance may result in a lethal increase in the volume of shunt as the blood follows the most favorable pressure gradient. In all these cases the intravenous use of nor-epinephrine (1 or 2 mg. in 500 cc. of 5 per cent glucose in water) or Neo-Synephrine (10 mg. in 500 cc. of 5 per cent glucose) is indicated. Since nor-epinephrine is rapidly destroyed in blood it is given into a vein other than the one receiving the transfusion.

The control of tachycardia in patients with mitral stenosis will also have a salutary effect on the blood pressure as outlined above. In certain selected cases in which bradycardia and hypotension appear the judicious intravenous use of ephedrine (30 to 50 mg.) may be indicated. It should be reserved for this specific situation, however, because of the risk of its producing a dangerous degree of cardiac irritability when these special conditions do not prevail.

Blood Replacement

Admonitions to replace blood loss should not be necessary in the current era of ready availability of whole blood. The enlarged heart of chronic rheumatic disease and severe mitral stenosis, however, tolerates hemorrhage so poorly that a minute-to-minute replacement is necessary. It is probable that sudden hemorrhage removes the stimulus for ventricular contraction that is present in a well filled chamber. For this reason, in all procedures in which there may be massive hemorrhage (procedures through the wall of the left ventricle and the lucite baffle procedure for mitral insufficiency[10]), an arterial transfusion is used so that adequate perfusion of the coronary vessels is assured. This procedure may also be useful in borderline cases of coronary insufficiency.

The sponge-weight method for the determination of blood loss has demonstrated its value, but we find that we are generally correct in our replacement if we exceed the measured loss by at least about 500 cc. Our early fears of overtransfusing the cardiac patient have never proved a major problem with the rough yardstick of sponge weight. This is tempered with clinical judgment and the knowledge that diminished blood volume is probably more injurious to the damaged myocardium than plethora, which can readily be corrected. Actually, there is probably a large area of relative safety between these two extremes.

At times during operation blood replacement may lag behind loss, and the usual tendency is to pump it into the vein with a syringe. In cardiac patients with congestive hepatomegaly or cirrhosis the resulting damage to red cells may release an amount of blood pigment that the liver is inadequate to metabolize. As a result the patients become jaundiced postoperatively. To avoid this complication pressure transfusion is now carried out by compression of the plastic bag containing the blood.[11] This technic has virtually eliminated postoperative jaundice.

Cardiac Irritability

The final major problems of the intraoperative phase are cardiac irritability, ventricular fibrillation and cardiac arrest. Experience with hundreds of patients abundantly demonstrates that safety lies in *prevention rather than treatment.* This prevention is complex and begins with the selection of the patient. It includes his optimal medical preparation, the bolstering of his confidence, proper premedication, impeccable anesthetic induction, ample pulmonary ventilation and careful, rapid surgery. In addition, the use of local anesthetics on the intercostal nerves be-

fore the ribs are spread helps prevent neurogenic cardiac irregularities.[12] Hypotension, with its attendant myocardial ischemia, is corrected by control of tachycardia, vasoconstrictors and blood replacement intravenously or intra-arterially as indicated.

Much cardiac irritability can be corrected preoperatively by the regulation of digitalis dosage. During operation runs of nodal or idioventricular rhythm, extrasystoles and atrial or ventricular tachycardia may appear when the pericardium is first opened and the heart handled. Many of these signs of irritability disappear as the heart adapts itself to this direct stimulation. Spontaneous acclimatization of the myocardium has given the erroneous impression in the past that procaine injected into the pericardial sac corrects irritability. Long ago the routine use of intrapericardial procaine was abandoned, and with it much undesirable myocardial depression avoided. If irritability does not disappear spontaneously 75 to 100 mg. of procaine amide (Pronestyl) may be given intravenously. Additional doses may be given after an interval of five to ten minutes if the abnormality is not corrected.

Ventricular Fibrillation

When ventricular tachycardia becomes ventricular fibrillation some method of bringing the heart into standstill and then initiating a co-ordinated beat is necessary. Unfortunately, no single technic or combination of technics affords completely reliable defibrillation. Our successful efforts have followed the intracardiac injection of procaine (10 cc. of 1 per cent solution) or potassium chloride[13] (10 milliequiv. in 10 cc.) to produce standstill. This is followed by vigorous manual systole to maintain the circulation until an adequate heart beat is restored. Calcium chloride[14] (10 cc. of a 10 per cent solution) has proved to be the most reliable agent for reviving the arrested heart. Epinephrine (1.0 mg. in 10 cc. of saline solution) is also useful, although it appears to have a somewhat greater tendency to result in a recurrence of ventricular fibrillation.

During all these resuscitative efforts, intermittent cardiac compression (incorrectly referred to as "cardiac massage") must be used to support the circulation and vigorous artificial respiration with 100 per cent oxygen through the endotracheal tube should be employed for oxygenation and removal of anesthetic agent and carbon dioxide. In addition compression of the descending aorta helps maintain the vital cardiac and cerebral circulation.

Electric shock undoubtedly has a place in cardiac defibrillation, but our experience in *adult patients with acquired heart disease* is not as convincing as that reported by others in children with congenital heart disease or in adults with normal hearts suffering ventricular fibrillation during operations in some other region of the body. Electric defibrillation is employed only when the simple measures described above have failed, for we have not encountered a single case in which the patient has survived defibrillation by this means.

This policy is based on laboratory as well as clinical experience. The Beck machine utilizing 110 volts and 1.5 amperes has not been satisfactory in this experience. In the laboratory, however, on dogs of moderate size, 150 volts (3 or 4 amperes for 0.5 second) succeeds in stopping ventricular fibrillation. Yet defibrillation is not resuscitation, and approximately 50 per cent of defibrillated hearts in dogs do not function adequately for survival despite epinephrine, calcium chloride, intermittent compression and other measures. The explanation may lie in the fact that pathological study of these defibrillated hearts generally reveals some myocardial necrosis. It is conceivable that a machine that would deliver 1000 volts (5 or 6 amperes for 1/100 to 1/500 of a second) might reduce the myocardial damage. An additional device that may prove useful in cardiac arrest and ventricular fibrillation is the artificial pacemaker of Zoll[15] although experience with it in the open chest is limited.

The duration of ventricular fibrillation is of vital importance, for the longer it persists, the more difficult its elimination. There are well documented cases in which transient fibrillation reverted spontaneously to normal rhythm. Although we have successfully defibrillated, with subsequent survival, a significant number of hearts by pharmacologic means it must be emphasized that in the adult heart suffering from long-standing acquired disease, the appearance of ventricular fibrillation is a catastrophic and terminal event in the majority of cases.

Probably fewer than 1 or 2 per cent of human hearts that have gone into persistent ventricular fibrillation have been satisfactorily defibrillated with ultimate survival of the patient. Therefore, it is repeated that the *best treatment for ventricular fibrillation is prevention.* When all the preventive measures mentioned are scrupulously practiced this serious problem seldom arises.

Cardiac Arrest

Uncomplicated cardiac arrest is a different and simpler problem. By limitation of the dose of ether to 15 to 30 cc. for a procedure lasting an hour and a half and with improved technics for controlling hemorrhage at the cardiotomy site, the incidence of cardiac arrest has been reduced to the vanishing point. If it does occur, however, simple measures are generally effective. The anesthetic agent is immediately washed out by hyperventilation with 100 per cent oxygen, and gentle intermittent cardiac compression is instituted. This alone frequently restores the beat. If actual arrest persists, however, 6 to 10 cc. of 10 per cent calcium chloride is injected directly into the left ventricle and stroked into the coronary circulation. This may be repeated, or 1.0 cc. of epinephrine (1:1000 solution) diluted with 10 cc. of saline so-

lution may be used similarly. With this routine resuscitation and survival are the rule. This is in marked contrast to the situation in persistent ventricular fibrillation.

If arrest occurs before a stenotic valve has been opened valvuloplasty is carried out as soon as possible after the beat has been restored. If the arrest occurs during the intracardiac manipulation the beat is restored as outlined above, and the manipulation stopped until the heart has had a chance to recover. Success in this crisis has undoubtedly been favored by a rapid completion of the operation as soon as the valve has been opened.

If cardiac arrest occurs when the chest is closed or in patients not under anesthesia one must consider an acute coronary occlusion, a pulmonary embolus and vagal arrest as etiologic agents. Under such circumstances the trauma of opening the chest may rob the patient of his last chance for survival. Furthermore, it must be borne in mind that an unobtainable pulse and blood pressure are not pathognomonic of cardiac arrest or ventricular fibrillation. This merely suggests "circulatory arrest." The electrocardiogram is useful in determining the actual state. Finally, if facilities for artificial ventilation with an endotracheal tube are not immediately available, the pneumothorax and open wound in the chest may present an insurmountable burden to the patient. Stimulation of the heart through the intact chest wall by a needle will revive spontaneous beating in many hearts suffering from vagal arrest. Calcium chloride and epinephrine solutions may be injected in the appropriate dilutions. If the arrest is not corrected by these simple measures and *overdosage of an anesthetic or drug can be definitely incriminated* the chest and pericardium must be opened and manual systole instituted. Without an accurate appraisal of the situation on clinical and electrocardiographic grounds, however, and without equipment for artificial respiration with 100 per cent oxygen, a great deal of harm may be done by the indiscriminate use of open thoracotomy and manual systole.

It has become too easy to excuse the violent act of emergency thoracotomy and manual systole by the statement that there was "nothing to be lost and everything to gain." In fact, far more often, a *coup de grâce* is rendered in a situation that should have been prevented, could better have been treated otherwise or did not exist in the first place.

Embolization

In valvular surgery on the left side of the heart one of the most important sources of morbidity and mortality is embolization. This may occur when clots are detached from the left atrium or when showers of calcific particles are loosened during the manipulation of the mitral or aortic valve. For the former, vigorous flushing of the atrium before the finger is inserted and the introduction of a large-bore suction tip within the chamber will remove many friable clots from the blood stream. In addition it is our practice to interrupt the circulation to the brain in all patients with mitral stenosis who are over the age of thirty-five, who are fibrillating or who have demonstrable calcium in their valves. This is also carried out in all operations for aortic stenosis because of the extremely high incidence of heavy, friable calcification in these cases. To this end rubber dam drains are passed about the right innominate, left common carotid and left subclavian vessels. The subclavian is also included because of a death due to an embolism of the basilar artery that occurred before the importance of this route was appreciated. During the dangerous portions of the intracardiac maneuver the circulation to the brain is interrupted by kinking of these vessels at their origins. The period of occlusion should be limited to one minute if possible and should almost never exceed a minute and a half. If longer periods of protection are needed a rest period of several minutes for re-establishment of cerebral flow should be allowed before another period of interruption. By this series of maneuvers the incidence of embolization has been significantly reduced but not entirely eliminated. Indeed, it appears unlikely that embolism during surgery will ever be entirely eliminated in patients with clotted atria and calcified valves.

(To be concluded)

References

1. Lown, B., Salzberg, H., Enselberg, C. D., and Weston, R. E. Interrelation between potassium metabolism and digitalis toxicity in heart failure. *Proc. Soc. Exper. Biol. & Med.* **76**:797-801, 1951.
2. Wilson, G. M., et al. Metabolic changes associated with mitral valvuloplasty. *Circulation* **9**:199-220, 1954.
3. Moore, F. D. Low sodium syndromes of surgery: outline for practical management. *J.A.M.A.* **154**:379-385, 1954.
4. Deming, Q. B., and Gerbode, F. Salt administration after mitral valvulotomy. *Ann. Surg.* **139**:143-148, 1954.
5. Gerbode, F. Discussion of "Electrolyte studies in pericardial resection." *J. Thoracic Surg.* **26**:486-507, 1953.
6. Harken, D. E., Ellis, L. B., Dexter, L., Farrand, R. E., and Dickson, J. F., III. Responsibility of physician in selection of patients with mitral stenosis for surgical treatment. *Circulation* **5**:349-362, 1952.
7. Lusk, J. A., Viar, W. N., and Harrison, T. R. Further studies on effects of changes in distribution of extracellular fluid on sodium excretion: observations following compression of legs. *Circulation* **6**:911-918, 1952.
8. Goodale, W. T., and Nadas, A. S. Personal communication.
9. Maloney, J. V., Jr., Derrick, W. S., and Whittenberger, J. L. Device producing regulated assisted respiration. II. Prevention of hypoventilation and mediastinal motion during intrathoracic surgery, *Anesthesiology* **13**:23-33, 1952.
10. Harken, D. E., Black, H., Dexter, L., and Ellis, L. B. Surgical correction of mitral insufficiency. *S. Forum* **4**:4-7, 1953.
11. Walter, C. W., and Murphy, W. B., Jr. Closed gravity technique for preservation of whole blood in ACD solution utilizing plastic equipment. *Surg., Gynec. & Obst.* **94**:687-692, 1952.
12. Burstein, C. L., Piazza, T. L., Kapp, L. A., and Rovenstine, E. A. Circulatory disturbances during intrathoracic surgery. *Surgery* **25**: 36-46, 1949.
13. Swan, H., Zeavin, I., Holmes, J. H., and Montgomery, V. Cessation of circulation in general hypothermia. I. Physiologic changes and their control. *Ann. Surg.* **138**:360-377, 1953.
14. Kay, J. H., and Blalock, A. Use of calcium chloride in treatment of cardiac arrest in patients. *Surg., Gynec. & Obst.* **93**:97-102, 1951.
15. Zoll, P. M. Resuscitation of heart in ventricular standstill by external electric stimulation. *New Eng. J. Med.* **247**:768-771, 1952.

CHRONIC DISCOID LUPUS ERYTHEMATOSUS*

Treatment with Daraprim and Chloroquine Diphosphate (Aralen)

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BOSTON, MASSACHUSETTS, AND PAWTUCKET, RHODE ISLAND

EVER since chronic discoid lupus erythematosus was first described in 1828 by Biett, there have been innumerable reports of its treatment.[1-4] Various methods have been advocated but none have proved successful in substantially significant numbers, and some have been associated with many severe toxic complications.

The first effective use of quinacrine hydrochloride in the treatment of discoid lupus erythematosus by Prokoptchouk,[5] and later by Page[6] and others, opened a new realm of therapy. Most authors have found that about 60 per cent of the cases either clear completely or are greatly improved on this medication.[7-9] The rationale of this drug has not been completely elucidated though many theories have been proposed as the mechanism of action.[10]

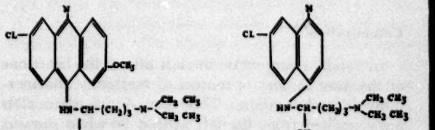
Quinacrine hydrochloride, however, has not been without many complications and toxic effects, and because of this fact the present study was undertaken. We first endeavored to see if another effective antimalarial drug whose pharmacology and mode of action were entirely different from that of quinacrine hydrochloride could be found. Secondly, we sought a less toxic drug, which would be as successful therapeutically. Daraprim and chloroquine diphosphate were selected. Since this study was started, Goldman et al.[11] and Farber and Driver[12] have reported small groups of cases treated with chloroquine diphosphate.

Daraprim** (5-[p-chlorophenyl]-2:4-diamino-6-ethylpyrimidine) is one of the 2:4 diaminopyrimidines, all of which are competitive antagonists of folinic acids in the growth of *Lactobacillus casei*. After the demonstration of the high antimalarial activity of Daraprim by Rollo and the toxicity tests of Beer, the first doses of the drug and allied compounds were taken by Goodwin[13,14] and his colleagues in 1950-51. Initially, 50 to 100 mg. was taken, with no side effects; then larger doses were used. Later clinical trials in cases of quiescent human malaria were conducted by Coatney et al.[15] in children five to ten years of age; subsequently, a field study by McGregor and Smith[16] was conducted in Gambia in 1951 on subjects with active malaria. They found that the drug was a powerful destructive agent on dividing schizonts and had a lesser and inconstant effect on trophozoites. The blood was free of asexual parasites within seventy-two hours in all but 2 cases of *Plasmodium falciparum* infection, and within ninety-six hours in all cases of *P. malariae* infection. In the treatment of malaria Daraprim has not been as successful as chloroquine phosphate, but it has been used for suppressive and prophylactic purposes.[17]

TREATMENT WITH DARAPRIM

Five patients with chronic discoid lupus erythematosus, representing both sexes and ranging in age from thirty-six to forty-nine years, were treated with Daraprim for two or three months. Initial doses were 25 mg. a week (as suggested for suppressive doses for malaria). The dose was then raised in two steps to 25 mg. a day. Two patients were under treatment for two months, and 3 for three months. Weekly clinical and laboratory examinations were made to evaluate the responses of the skin lesions and any toxic effects of the drug used. No changes were seen in the skin lesions in 3 of the patients at any time during our evaluations, whereas in 2 there was slight improvement, with fading and regression at the edges of the lesions; however, both these patients soon relapsed, and there was little change in their total picture. After stopping Daraprim 4 patients were placed on chloroquine diphosphate and showed a dramatic response.

Quinacrine hydrochloride (Atabrine), whose exact chemical name is 3-chloro-7 methoxy-9 (1-methyl-4-diethylaminobutylamino) acridine dihydrochloride dihydrate, has a structural formula somewhat similar to that of chloroquine:



Chloroquine, which has the formula 7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline, is mar-

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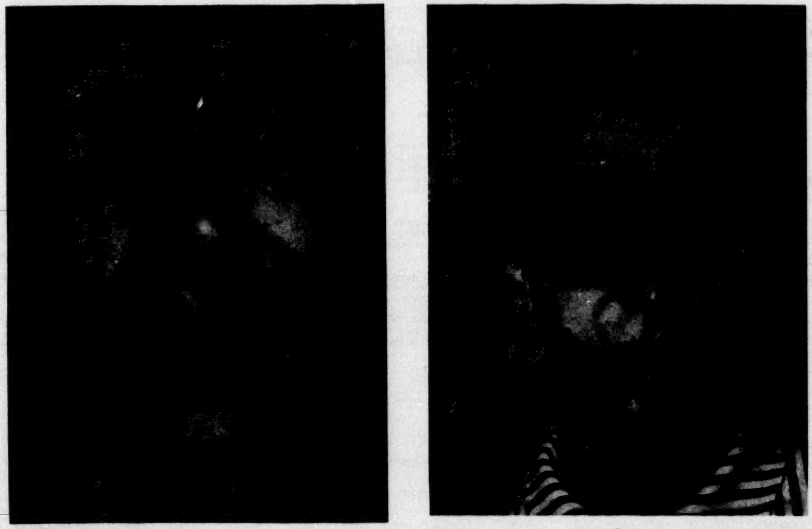
TABLE 1. *Results of Chloroquine Therapy in 25 Cases.*

PATIENT	AGE	SEX	RACE	DISTRIBUTION OF LESIONS	DURATION OF DISEASE	PREVIOUS THERAPY	DURATION OF CHLOROQUINE TREATMENT	UNTOWARD REACTION	RESULT
Schedule 1*:	yr.				yr.				
J.W.	49	F	W	Chest & cheeks	2½	Daraprim	3 mo.	None	Complete clearing
A.McL.	40	M	W	Cheek & lips	9	Gold, bismuth, liver, arsenic, isonicotinic hydrazide & Daraprim	7 mo.	None	Complete clearing of lesions, with slight recurrence after 1 wk. of cessation of treatment; clearing after retreatment.
M.W.	44	M	W	Face	21	Bismuth, gold, Daraprim & carbon dioxide locally	7 mo.	Headaches on 3 tablets; headaches stopped on 2 tablets.	Great improvement
S.G.	36	F	W	Scalp, face, arms, neck & chest	18	Bismuth, gold, calcium, liver, streptomycin, carbon dioxide, penicillin, ACTH, isonicotinic hydrazide & Daraprim	6 mo. (2 interruptions)	None	Improvement
D.K.	41	F	W	Nose & ears	?	None	6 mo.	Dizziness & diplopia & anorexia on 2 tablets; cleared on 1 tablet & 2 tablets alternated daily.	Great improvement
F.F.	60	M	W	Face	?	Local medication	2½ mo.	None	Complete clearing
O.J.B.	33	M	W	Face, arms, shoulders & neck	5	"Pills" & local treatment	5 mo.	None	Good improvement
M.G.B.	60	M	W	Face, scapula & neck	20	Carbon dioxide, x-ray, gold etc., cortisone, PABA etc.	5 mo.	None	Almost complete clearing of lesions
A.D.	38	F	W	Face	4	Bismuth	1 mo.	None	Clearing of lesions
A.N.	55	F	W	Arms & chest	½	None	3 mo.	None	Great improvement
B.S.	29	F	W	Face, scalp & ears	8	Bismuth & gold; vitamin B_{12}	4 mo.	None	Great improvement
G.D.	40	M	W	Face & scalp	1½	Bismuth & gold	3 mo.	None	Clearing of lesions
F.W.	50	F	W	Face & scalp	4	Carbon dioxide & local treatment	5 mo.	None	Great improvement
Schedule 2†:									
L.B.	32	M	W	Face & lip	8	Gold & mephenesin calcium	2 mo.	None	Clearing of lesions; treatment stopped for 7 mo., with no recurrence.
K.R.	50	M	W	Scalp, face & lip	4	Gold & bismuth	7 wk.	None	Clearing of lesions in 4 mo.; treatment stopped.
V.L.	53	M	W	Face	3	Carbon dioxide	7 wk.	None	Clearing of lesions; recurrence few weeks after treatment stopped.
M.F.	43	M	W	Nose	2	Gold	7 wk.	None	Clearing of lesions
H.A.	49	F	W	Face & chest	2½	Gold	7 wk.	None	Great improvement
D.B.	43	M	W	Cheeks & scalp	2½	None	8 wk.	None	Clearing of lesions of face; those of scalp improved.
B.M.	35	F	W	Face & arms	3	Topical applications	5 wk.	None	Great improvement
C.O.	60	M	W	Nose	4	Topical applications	6 wk.	None	Clearing of lesions; treatment stopped.
C.S.	31	M	W	Face	2½	None	6 wk.	None	Clearing of lesions
C.E.	38	M	W	Face & retroauricular areas	6	Bistrimate	6 wk.	None	Clearing of lesions
C.S.	32	M	W	Face & scalp	7	Rimifon & cortisone	7 wk.	None	Great improvement
C.A.	55	M	W	Nose	14	None	7 wk.	None	Improvement
C.J.	31	M	W	Face	5	Bismuth & carbon dioxide	6 wk.	None	Clearing of lesions

*One tablet 4 times daily for 2 days, 1 tablet 3 times daily for 2 days & then 1 tablet twice daily.
†One tablet 3 times daily for 2 wk., 1 tablet twice daily for 1 wk. & then 1 tablet daily as maintenance dose.



A B

FIGURE 1. *Appearance of a Patient with Discoid Lupus Erythematosus before* (A) *and Appearance Two Months after* (B) *Treatment with Chloroquine Diphosphate Was Started.*

A B

FIGURE 2. *Appearance of a Patient with Chronic Discoid Lupus Erythematosus of Four Years' Duration before Treatment* (A) *and after* (B) *Treatment for Forty-Two Days Showing Clearing of Lesions, with Slight Residual Pigmentation.*

keted in the phosphate form under the trademark of Aralen phosphate tablets of 0.25 gm. (equivalent to 0.15-gm. base). Chloroquine is deposited in the organs and tissues, being concentrated in the nucleated cells of the liver, spleen, kidneys and lung and also to a considerable extent in leukocytes. It is metabolized in the body, only a small part being found in excreta. The concentration of the drug in the body fluids generally falls about 60 per cent a week after treatment has been discontinued.[18]

Treatment with Chloroquine

Toxicologic studies on chloroquine have been done by Alving et al.,[19] who gave it in doses of 500 mg. weekly for a year to 30 men, 2 of whom manifested eruptions similar to lichen planus after eight and twelve months. This eruption cleared on discontinuation of the drug and did not reappear on readministration. Except for 1 case patients in whom these eruptions followed quinacrine therapy did not have exacerbations of the dermatitis on chloroquine therapy.[20] Alving et al.[21] kept 20 men on 0.3 gm. of chloroquine base daily for seventy-seven days and then on 0.5 gm. weekly for a year, and at the same time they treated another group with 0.5 gm. of chloroquine weekly for a year. They noted visual abnormalities, consisting of difficulty in changing focus quickly from a near to a far object, in half those on the daily dosage. The tests for visual acuity, power of monocular accommodation and diplopia failed to demonstrate objective abnormalities. Electrocardiographic changes of concordant diminution of height of the T wave in some leads and bleaching of hair in blonds near the roots were noted. All these symptoms and signs cleared as the dosage was lowered. Headache and weight loss were noted in a few cases.

Twenty-six patients with chronic discoid lupus erythematosus have been treated with chloroquine diphosphate (Aralen) for periods of five weeks to seven months. Both sexes are represented, ranging in age from thirty-one to sixty years. One patient was a Negro; the rest were white. Two dosage schedules were used. On the first, 12 patients were treated with 1 tablet, 0.25 gm. each, four times daily for two days, 1 tablet three times daily for two days and then 1 tablet twice a day; the dosage was then dropped in some cases to 1 tablet daily as the lesions cleared or were greatly improved. The remaining 13 patients were given 1 tablet, 0.25 gm. each, three times a day for two weeks, 1 tablet twice a day for one week and then 1 tablet daily as a maintenance dose (Table 1).

Complete blood counts were done weekly, as well as urinalyses, none of which showed any change attributable to treatment. Cephalin flocculation was tested in 10 patients after a month of treatment, with no abnormal findings.

Three patients had side reactions. One had headaches on 3 tablets a day; another complained of nausea and dizziness while receiving 3 tablets a day, and a third had nausea, dizziness and diplopia on 2 tablets a day. All symptoms disappeared when the dosage was decreased. No abnormal laboratory changes were noted in any of these cases.

Treatment was stopped in 8 patients after involution of all lesions. Three of these had recurrences and were placed on maintenance therapy. The remaining 5 have been off treatment for periods of three to seven months without recurrence. Seven more patients had complete involution of all lesions and are still on maintenance therapy. All other patients have shown progressive improvement continuing for six and seven months after onset of treatment. The greatest degree of improvement seemed to occur in the first month in some cases, and the rate of progress was slow but gradual for several weeks thereafter. Typical responses are shown in Figures 1 and 2.

Summary

Five patients with chronic discoid lupus erythematosus were treated with Daraprim, an antimalarial drug, for three months without any objective evidence of improvement.

Twenty-six patients were treated with chloroquine diphosphate (Aralen). In 13 the lesions have completely cleared, and all others have shown improvement.

Since this report was submitted for publication 22 patients have completely cleared and remained so after stopping treatments for periods varying from a few weeks to several months. Four patients have continued to show progressive improvement but are still being treated.

Two patients, 1 with blond and 1 with red hair, have had the color of their hair made lighter.

References

1. Tolman, M. M. Lupus erythematosus discoides. *New Eng. J. Med.* 219:688-697, 1938.
2. Goldman, L. New developments in treatment of chronic discoid lupus erythematosus. *M. Clin. North America* 35:391-398, 1951.
3. Stokes, J. H., Beerman, H., and Ingraham, N. R., Jr. Lupus erythematosus concept: attempt at integration. *Am. J. M. Sc.* 207: 540-549, 1944.
4. Appel, B., Baler, G. R., and Dougherty, E. F. Isoniazid in treatment of chronic lupus erythematosus. *Arch. Dermat. & Syph.* 68:417, 1953.
5. Prokoptchouk, A. J. Traitement du loup érythémateux par l'acriquine. In *Year Book of Dermatology and Syphilology.*[20]
6. Page, F. Treatment of lupus erythematosus with mepacrine. *Lancet* 2:755, 1951.
7. Cramer, J. A., and Lewis, G. M. Atabrine in treatment of discoid lupus erythematosus. *J. Invest. Dermat.* 19:393-395, 1952.
8. Sawicky, H. H., Kanof, N. B., Silverberg, M. G., Braitman, M., and Kalish, B. Therapeutic Assays of Skin and Cancer Unit of the New York University Hospital. Assay VII. Quinacrine hydrochloride (atabrine hydrochloride) for chronic discoid lupus erythematosus. *J. Invest. Dermat.* 19:397-404, 1952.
9. Wells, G. C. Treatment of chronic discoid lupus erythematosus with atabrine. *J. Invest. Dermat.* 19:405-407, 1952.
10. *Year Book of Dermatology and Syphilology.* Edited by M. B. Sulzberger and R. L. Baer. 444 pp. Chicago: Year Book Publishers, 1952. P. 92.
11. Goldman, L., Cole, D. P., and Preston, R. H. Chloroquine diphosphate in treatment of discoid lupus erythematosus. *J.A.M.A.* 152:1428, 1953.
12. Farber, E. M., and Driver, I. E. Atabrine and chloroquine in treatment of chronic discoid lupus erythematosus: preliminary report. *Stanford M. Bull.* 11:157, 1953.
13. Goodwin, L. G. Daraprim-clinical trials and pharmacology. *Tr. Roy. Soc. Trop. Med. & Hyg.* 46:485, 1952.
14. *Idem.* Daraprim (B.W. 50-63) — new antimalarial: trials in human volunteers. *Brit. M. J.* 1:732-734, 1952.
15. Coatney, G. R., et al. Studies on compounds: 50-63. *Tr. Roy. Soc. Trop. Med. & Hyg.* 46:496, 1952.
16. McGregor, I. A., and Smith, D. A. Daraprim in treatment of malaria: study of its effects in falciparum and quartan infections in West Africa. *Brit. M. J.* 1:730, 1952.
17. Fairley, N. H. Symposium on Daraprim: discussion. *Tr. Roy. Soc. Trop. Med. & Hyg.* 46:504, 1952.
18. Osol, A., and Farar, G. E., Jr. *The Dispensary of the United States of America.* P. 1342. Philadelphia: Lippincott, 1947.
19. Alving, A. S., et al. Lichen-planus-like eruption occurring during course of chloroquine administration. *J. Clin. Investigation* 27: 56, 1948.
20. Most, H., et al. Chloroquine for treatment of acute attacks of vivax malaria. *J.A.M.A.* 131:963-967, 1946.
21. Alving, A. S., et al. Studies on chronic toxicity of chloroquine (SN-7618). *J. Clin. Investigation* 27:60-65, 1948.

SYSTEMIC BLASTOMYCOSIS*

Cause of an Obscure Infection in a Nonendemic Area

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PHILADELPHIA

THE occurrence of a case of an infectious disease in a geographic location outside an area recognized as endemic is always of clinical interest. Diseases hitherto associated with arbitrary geographic boundaries must now be considered more frequently in the differential diagnosis of obscure infections.[1,2] The purpose of this presentation is to report a case of systemic blastomycosis in Philadelphia and to demonstrate some of the unusual features concerning the difficulties in diagnosis and management, the rapidity of the clinical course and the failure of response to specific therapy.

CASE REPORT

J.F., an 18-year-old Negro, was admitted to the St. Luke's and Children's Medical Center on June 8, 1953, because of a 3-week history of a "chest cold" with fever, chills, chest pain, sweating and a cough that at first was nonproductive but later became slightly productive of blood-tinged sputum; this had failed to respond at home to penicillin. An x-ray film of the chest taken at a chest clinic before admission was reported to show a large area of pneumonic consolidation involving practically the entire right upper lobe.

The past and family histories, and a review of the systems were noncontributory. There was no history of tuberculosis in the family or any outside contacts. The patient worked as a farmhand in North Carolina and had only recently moved to Philadelphia.

Physical examination revealed a well developed, well nourished Negro who appeared quite ill. The significant physical findings were limited to the right upper portion of the chest anteriorly, where there were dullness, bronchial breath sounds, and many medium rales. There was no detectable lymphadenopathy. The heart was not enlarged, but there was a tachycardia, as well as a Grade 1, soft, apical systolic murmur.

The temperature was 103°F., the pulse 120, and the respirations 20. The blood pressure was 118/80.

A roentgenogram of the chest (Fig. 1) showed a large area of pneumonic consolidation that, on comparison with the film taken previously, gave the impression of a resolving pneumonic process involving practically the entire right upper lobe. A zone of radiolucency within the infiltration suggested cavity formation. A small area of infiltration was also seen at the right cardiophrenic sulcus. The hemoglobin was 10.0 gm. per 100 cc., and the white-cell count 25,000, with 90 per cent segmented neutrophils, 5 per cent lymphocytes, 4 per cent monocytes and 1 per cent eosinophils. Urinalysis, serologic tests for syphilis and stool cultures were negative. The total serum protein, albumin-globulin ratio and renal-function studies were all within normal limits. An electrocardiogram revealed a sinus tachycardia. Tuberculin tests with P.P.D. in 1st and 2d strengths were negative.

The patient progressively failed, with anorexia and weight loss during the next 5 weeks in spite of the various therapeutic measures adopted. The temperature fluctuated daily between 99 and 104°F. The hemoglobin dropped to 8 gm. per 100 cc. Repeated chest films showed no change in the appearance of the infiltration, but reticulation was noted throughout both lung fields and a suggestion of hilar adenopathy. Numerous sputum cultures were negative for both routine pathogenic organisms and acid-fast bacilli. Many diagnostic possibilities were considered, and appropriate laboratory procedures were carried out for virus pneumonia,

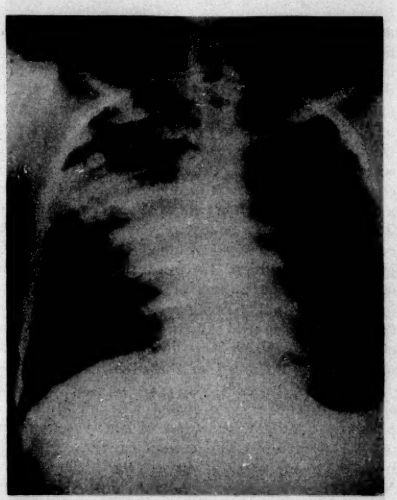

FIGURE 1. *Roentgenogram of the Chest Taken on June 8.*

pulmonary tuberculosis, tularemia, typhoid, lupus erythematosus, carcinoma, brucellosis, sarcoidosis, histoplasmosis, coccidioidomycosis and blastomycosis. The various antibiotics, sulfonamides, streptomycin and PAS failed to bring about any improvement. On July 8 a course of cortisone, 25 mg. every 6 hours, was instituted. The temperature dropped to normal for 24 hours but then went up to 103°F. thereafter. On July 16 the patient complained of a painful, tender left knee; within the next few days this became red and swollen. A joint paracentesis was performed on July 20, and approximately 100 cc. of purulent material was removed. Smears of the aspirate revealed budding, yeastlike cells resembling *Blastomyces dermatitidis*. Arrangements were made for transfer to the Philadelphia General Hospital, and the patient was discharged on July 25.

He failed to comply with the arrangements, and was admitted to the Temple University Hospital on July 27, with the complaints of fever, chills and a painful, swollen left knee. Upon admission it was noted that he was mentally dull and had a marked motor speech defect, which the family stated that he had had from childhood. The

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temperature was 103°F., the pulse 150, and the respirations 20; the blood pressure was 124/70. There was mild injection of the posterior tonsillar pillars, and a yellowish white exudate over the posterior pharynx. Examination of the lungs revealed dullness, bronchial breath sounds and medium rales over the right upper part of the chest anteriorly, and dullness and decreased breath sounds, tactile fremitus and vocal resonance at the base of the left lung posteriorly. The heart was not enlarged. There was a Grade 2, soft, short apical systolic murmur and a tachycardia. Examination of the abdomen and extremities, with the exception of the painful swollen left knee, was negative. The deep tendon reflexes were active and equal.

The hemoglobin was 10.8 gm. per 100 cc., the hematocrit 36 per cent and the white-cell count 20,900, with 88 per cent segmented neutrophils, 2 per cent band forms, 9 per cent monocytes and 1 per cent lymphocytes. Urinalysis, serologic tests for syphilis, 3 blood cultures and repeated specimens of sputum for acid-fast bacilli were negative. Direct smears of the sputum and synovial fluid from the left knee joint were positive for yeastlike organisms resembling *B. dermatitidis*. Aerobic and anaerobic cultures of the synovial fluid were sterile. The blood urea nitrogen was 13 mg., the alkaline phosphatase 4 Bodansky units, and the total serum protein 6.0 gm. per 100 cc. with 3.0 gm.

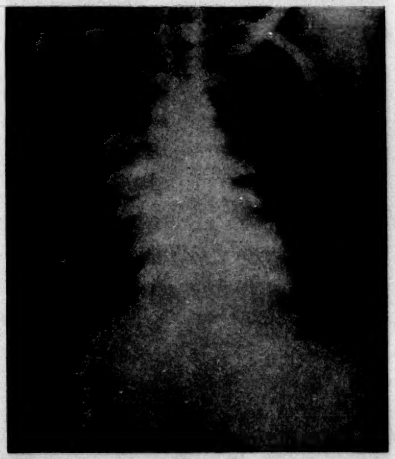


FIGURE 2. *Roentgenogram of the Chest Taken on July 31.*

per 100 cc. of albumin. The van den Bergh reaction was 0.38 mg. per 100 cc. indirect; the thymol turbidity was 0.9 units. The prothrombin time was 40 per cent, cephalin flocculation ++, and the serum cholesterol 134 mg. per 100 cc., with 58 per cent esters. There was one L.E. cell per 500 leukocytes examined. The urea clearance was 79.5 per cent and the creatinine 1.2 mg. and the serum uric acid 3.6 mg. per 100 cc. Sputum cultures, aerobic and anaerobic, were positive for many neisseria, pneumococci and *Streptococcus viridans*, as well as a moderate number of coliformlike organisms. X-ray study of the chest on July 31 (Fig. 2) demonstrated diffuse areas of increased opacity throughout both lung fields, with a triangular area of infiltration in the posterior segment of the right upper lobe. An x-ray film of the left knee (Fig. 3) revealed increased bone density about the joint, with effusion and several areas of osteolytic bone lesions. An intravenous pyelogram was normal, and an electrocardiogram disclosed a sinus tachycardia.

During the 1st 11 hospital days the temperature was elevated to 103 or 105°F. once or twice a day, subsequently falling to and remaining between 99 and 100°F., by rectum, during the last 7 hospital days. The respiratory rate was usually 20 to 40 a minute until the last 5 days, when it increased to 50 to 60. The patient continued to appear quite toxic, had a relatively nonproductive cough and frequently complained of pain below the sternum and in the left upper lobe, particularly when he coughed. On August 10, a joint paracentesis resulted in 95 cc. of creamy,

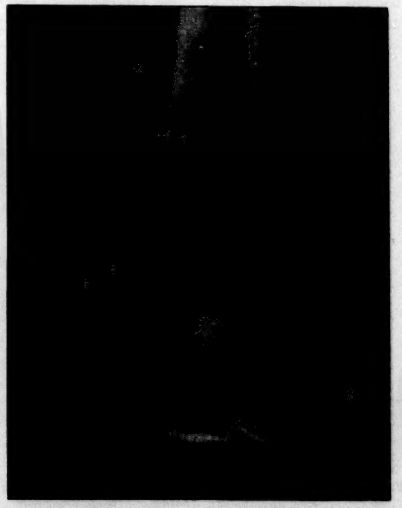


FIGURE 3. *Roentgenogram of the Left Knee Taken on July 31.*

yellow fluid, smears and cultures of which were positive for *B. dermatitidis*. A spinal tap revealed an acellular crystal clear spinal fluid under normal pressure, with normal chemical, serologic and bacteriologic findings. A repeat x-ray film of the chest demonstrated marked extension of the pathologic process throughout both lung fields. The blastomycin skin test was negative after 48 hours. Complement fixation was negative for histoplasma and coccidioides and positive for blastomyces in a dilution of 1:16.

Treatment consisted of bed rest and symptomatic measures at first. On July 30 a 15-day course of stilbamidine was instituted. The initial dose was 50 mg. in 200 cc. of 5 per cent glucose in saline infusion intravenously. Subsequent daily increments to 75 mg., 100 mg. and then 150 mg. in the same vehicle were administered for the remainder of the course. After the 5th dose toxicity appeared less noticeable although the tachypnea and tachycardia persisted and the joint effusion was reaccumulating. Rales were heard at the right base. Oxytetracycline, 1 gm. a day intravenously, was started on August 8 to control any secondary bacterial infection, and the patient appeared to improve temporarily. The temperature fell to 100°F. by rectum. However, on August 11, the respiratory rate increased to 50 to 60 a minute, and he appeared moribund. X-ray study of the chest (Fig. 4) revealed further marked, widespread involvement of all lung fields. Cortisone, 300 mg. each day intramuscularly, was started. Initially, he became more alert, his appetite increased, and he remained afebrile, although the chest pain and respiratory distress per-

sisted. Within 2 days his clinical condition became worse, and on August 15 he died.

At autopsy the heart, pericardium and great vessels were grossly normal. A section through the myocardium (Fig. 5) toward the base showed a focal area of infection that was yellowish white, of the same consistence as the surrounding muscle and 3 cm. in diameter. The mucosa lining the trachea and both bronchi was deeply hemorrhagic, and the distal bronchi contained considerable amounts of mucinous secretion. The left lung weighed 1150 gm., and the right 1250 gm.; both were completely and diffusely consolidated with miliary lesions measuring up to about 1 mm. in diameter (Fig. 6). These lesions, which were round and white, in all respects resembled miliary tubercles. Here and there in both lungs there were larger areas that had broken down and begun to cavitate. The liver weighed 1900 gm. and demonstrated considerable congestion, but there was no evidence of infection. The spleen weighed 150 gm. and had numerous old fibrous adhesions about the entire capsule; on section a 2.5-cm. developing abscess was found immediately under the capsule. The kidneys weighed 175 gm. each and were moderately swollen, but no focal areas of infection were found. The pancreas showed post-mortem autolysis. Examination of the gastrointestinal and genitourinary tracts, the testes, adrenal, thyroid and pituitary glands and brain was negative. The blastomyces organism was demonstrated in the sections from the heart, lungs, spleen and left knee joint.

FIGURE 4. *Roentgenogram of the Chest Taken Five Days before Death.*

DISCUSSION

North American blastomycosis is a chronic infection caused by *B. dermatitidis*. Most cases are concentrated in the southeastern United States and in the Mississippi River valley. Isolated cases are found throughout the United States and in eastern and western Canada. There have been 2 cases of this disease at the Philadelphia General Hospital during the past five years,[5] no other cases being reported in the State of Pennsylvania during that time.[4] The incidence of these isolated cases is becoming higher as more people are traveling about the country either in the military service or for business or pleasure. It should be emphasized that in the diagnosis of any of the mycotic diseases one should ascertain the residence of the patient for the previous five years, especially for the two or three months before the onset of symptoms. The patient described above was a native of North Carolina until approximately three months before the symptoms appeared.

Systemic blastomycosis is one of the most serious of the fungous diseases. Although such disorders are now recognized more frequently than they were a decade ago the systemic form of blastomycosis is notoriously difficult to diagnose. Even with a high index of suspicion and all the available bacteriologic facilities the correct diagnosis is often overlooked. This is particularly true when the acutely ill patient is rapidly failing.

FIGURE 5. *Photomicrograph of a Granuloma in the Myocardium (Hematoxylin and Eosin Stain X200). In the center there are several large giant cells containing numerous organisms.*

The onset of the illness in the case reported above, as in most of the typical cases of systemic blastomycosis, was insidious and began as a subacute respiratory infection. A pneumonic process developed but failed to respond to several different courses of anti-

biotics. The initial clinical picture resembled an ordinary bacterial, viral or rickettsial infection of the lungs. After the condition persisted tuberculosis, neoplasm and collagen disease were suspected. The patient presented a diagnostic and therapeutic problem that was not solved until after the onset of an acute septic arthritis in the left knee. Although the clinical picture was typical of blastomycosis, with the respiratory infection, dry, hacking cough, chest pain and later the purulent blood-streaked sputum, the high temperature, the great loss of weight and strength and the night sweats—the appearance of the acute arthritis per se did not further suggest this disease.

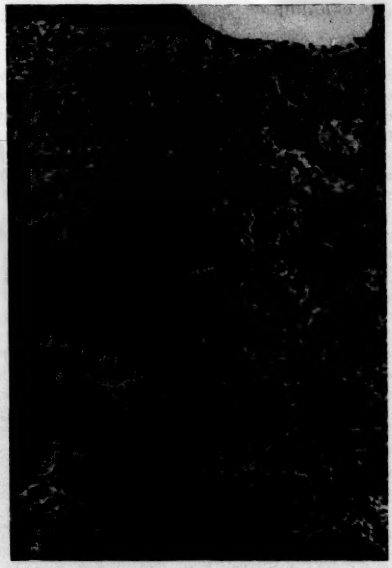


FIGURE 6. *Photomicrograph of a Granuloma in the Lung (Hematoxylin and Eosin Stain X200).*

There are central necrosis, epithelioid cellular reaction at the periphery and several giant cells. (Note the double-contoured organisms in the giant cells and contiguous tissue.)

The incidence of bone and joint involvement in systemic blastomycosis was 50 per cent in 243 proved and presumptive cases reviewed by Martin and Smith[5] in 1939; — in only 7 of these was the knee joint involved. Jones and Martin[6] reported 11 cases of involvement of the knee joint in a review of 63 cases of blastomycosis with bone and joint disease in 1941. In 13 the initial complaint was arthritic pain in the back or in one of the peripheral joints. Blastomycosis is not a common etiologic agent in acute septic arthritis. It is not mentioned as one of the etiologic factors in Comroe's[7] book or in the list of causes of arthritis in tropical diseases by Morgan and Comroe[8] in which other mycotic infections are considered. The infection reaches the joint by extension from a focus in the adjacent bone through the synovium or cartilage. In bone the process is usually a localized or diffuse osteomyelitis or periostitis. The fungous invades the bone-marrow compartments, with the usual cellular reaction, necrosis of marrow cells and bone destruction. X-ray study of the long bones and the spine demonstrates well localized, sharply defined processes in the metaphysis. When multiple these suggest blastomycosis, but single lesions may be confused with tuberculous osteomyelitis, a primary osteoclastic tumor (such as Ewing's sarcoma) or a gumma.

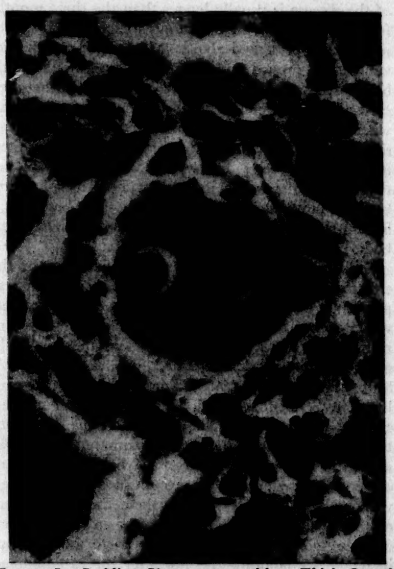


FIGURE 7. *Budding Blastomycete, with a Thick Capsule Seen in a Giant Cell within a Granulomatous Nodule in the Spleen (Hematoxylin and Eosin Stain X1464).*

After the joint paracentesis and the bacteriologic examination of the aspirated fluid the diagnosis in the case reported above became apparent but not conclusive. According to Jones and Martin[6] the demonstration of the organism should be supported by a skin test with the blastomyces antigen, complement fixation, culture of the organism and study of material removed by biopsy or autopsy. The diagnosis in the case described above was supported by all these criteria except for the skin test, which may be negative in the initial stages of the infection or in rapidly advancing cases.

The organism (Fig. 7), when seen on direct microscopical examination of material from cutaneous

lesions, subcutaneous abscesses, joint fluid, sputum, urine or spinal fluid, appears as single or budding spherical cells, 8 to 15 microns in diameter, with a refractile wall thick enough to give the forms a double-contoured appearance in fresh preparations. The infected material may be cultured on blood-agar, beef-infusion agar or on Sabouraud's glucose-agar slants, and gives a growth resembling a tuft of white cotton.

Although the mortality in the systemic form of blastomycosis is 92 per cent in patients who have been followed for two years or more the average duration of the disease is usually longer than the three months from the onset of the symptoms to the time of death in the case presented above. Martin and Smith,[5] reviewing 77 proved and presumptive cases of systemic blastomycosis, reported that 32 patients died between six and twelve months after the onset of symptoms, whereas only 20 had a clinical course of less than six months. The combination of a high antibody titer, indicating extensive disease, and a negative skin test suggesting anergy, as in our patient, usually forebodes a fatal outcome. The prognosis is better in a hypersensitive patient without complement-fixing antibodies in the serum.

Stilbamidine is apparently a specific drug for the treatment of this disease. It was first successfully employed by Schoenbach et al.[9] in 1951. Three patients with systemic blastomycosis had beneficial results with stilbamidine, and a fourth, in whom therapy could not be completed, demonstrated encouraging results.[10] Stilbamidine therapy, according to the program outlined by Schoenbach and his co-workers,[9,10] was instituted in our patient nine days after the first identification of the organism, or approximately nine weeks after the onset of symptoms. Myhr[11] reported another case of systemic blastomycosis successfully treated with stilbamidine. Review of these therapeutic successes reveals that the clinical course in all was more chronic and less fulminant than that in our patient, in whom stilbamidine did not alter the rapid spread of the infection. Recently, successful results in 3 cases of the systemic form and 1 case of the cutaneous form of blastomycosis, 2-hydroxystilbamidine being used, were reported by Snapper and McVay.[12] This agent is comparable to stilbamidine in its effect against *B. dermatitidis;* however, its solution is more stable, and larger dosages can be employed before signs of toxicity are manifested.

Summary

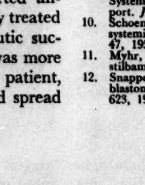
An acute fulminating case of systemic blastomycosis with a fatal outcome is presented. The patient, a native of North Carolina, had moved to Philadelphia three months before the onset of the illness.

Some of the unusual features of this case, including the diagnostic difficulties, management and failure to respond to therapy with stilbamidine are discussed.

We are indebted to Drs. William A. Steiger and R. V. Cohen for their suggestions in the preparation of the manuscript, to Drs. A. E. Aegerter and E. S. Gault for their review of the pathological material and preparation of the photomicrographs, and to Mr. William Taylor for the photographic reproductions.

References

1. Smith, D. T. Diagnosis and therapy of mycotic infections. *Bull. New York Acad. Med.* **29**:778-795, 1953.
2. Spitz, L. J., and Schwartz, B. Histoplasmosis in non-endemic regions. *Am. J. Med.* **15**:624-632, 1953.
3. Israel, H. Personal communication.
4. Purvis, R. L. Personal communication.
5. Martin, D. S., and Smith, D. T. Blastomycosis (American blastomycosis, Gilchrist's disease): review of literature. *Am. Rev. Tuberc.* **39**:275-304, 1939.
6. Jones, R. R., Jr., and Martin, D. S. Blastomycosis of bone: review of 63 collected cases, of which 6 recovered. *Surgery* **10**:931-938, 1941.
7. Comroe, B. I. *Arthritis and Allied Conditions.* Fourth edition. 168 pp. Edited by J. L. Hollander. Philadelphia: Lea and Febiger, 1949.
8. Morgan, J., and Comroe, B. L. Brief review of arthritis and allied conditions in tropical diseases. *Ann. Int. Med.* **24**:233-240, 1946.
9. Schoenbach, E. B., Miller, J. M., Ginsberg, M., and Long, P. H. Systemic blastomycosis, treated with stilbamidine: preliminary report. *J.A.M.A.* **146**:1317, 1951.
10. Schoenbach, E. B., Miller, J. M., and Long, P. H. Treatment of systemic blastomycosis with stilbamidine. *Ann. Int. Med.* **36**:31-47, 1952.
11. Myhr, L. B. Systemic blastomycosis: report of case treated with stilbamidine. *Am. Pract.* **5**:64-66, 1954.
12. Snapper, I., and McVay, L. V. Treatment of North American blastomycosis with 2-hydroxystilbamidine. *Am. J. Med.* **15**:603-623, 1953.



SPECIAL ARTICLE

SPECIALTY PRACTICE*

LELAND S. McKITTRICK, M.D.†

BOSTON

SPECIALISTS are a by-product of the science of medicine. As medicine has advanced, the opportunities offered for investigation of disease and methods of treatment have increased, and the knowledge gained in the various special fields has become so unlimited that specialization or special technics have become necessary. That this logical and necessary trend should progress to the present state of almost complete fragmentation of the human body into systems or anatomic areas could hardly have been anticipated. How far specialization has developed and how absurd it may appear is well illustrated by an incident that occurred recently in a well known teaching institution (this came to my attention not through the usual medical channels but through a discussion group of Blue Shield executive directors). In a discussion of the method of division of the total fee when more than one surgeon was involved in a given operation the following incident was given as an example of the problem: a general surgeon in a New England hospital had made a diagnosis of acute appendicitis, but when the abdomen was opened it was found that the patient had an ovarian cyst with a twisted pedicle rather than appendicitis. This condition, of course, fell within the field of gynecology. According to the rules of the hospital the general surgeon was not allowed to do gynecologic operations. It was necessary to call in a gynecologist to remove this ovarian cyst! The surgeon was then permitted to remove the appendix and close the abdomen. This concept of specialization is difficult to justify, but it is evidence of the degree of departmentalization that may occur under the conditions of specialization as it is now known.

If this is accepted as an absurdity, how could it have come about? If specialization is important and desirable, has the trend gone too far? At least a partial answer to these questions may be suggested by a review of the development of the specialty boards.

SPECIALTY BOARDS

According to the laws of most, if not all, states there is no distinction among practicing physicians. Dr. Jones, who went into practice immediately after graduation from medical school, is legally privileged to do any operation he may choose if he can get the patient's consent and obtain hospital facilities. Formerly, the public had no access to any information about the training, experience and ability of a given physician in his specialty. It therefore seemed logical and desirable that some means be established to set up minimum criteria for recognition in various specialized fields. Thus, in 1916, the first specialty board was organized. Today every graduate of a medical school who decides to go into a specialty looks forward to the time when he may receive certification in the specialty of his choice, and plans his training program accordingly.

However, with the development of more and more specialty boards, training programs have been more demanding. Many of them are now so long that candidates are shunted from a thorough training in the fundamentals of good medicine or surgery into special fields, to the degree that, at present and probably in a large measure owing to these boards, medicine has become so highly specialized that many young men and women are becoming specialists without adequate knowledge of the basic problems in general medicine and surgery.

Specialization, then, is a development of modern medicine. Although essential for the care of patients according to present knowledge of disease and present technical skills, it has been carried to extremes. Will the trend toward more and more specialization continue, or has the pendulum made its full swing, with an inevitable return to a closer co-ordination of the specialties with general medicine and surgery?

Most of the problems that arise after a hysterectomy are basically the same as those that follow a subtotal resection of the stomach. The knowledge necessary to recognize and care for each patient is similar. To be sure, certain problems are peculiar to each group of patients, but the basic principles involved in their surgical care are the same. The so-called general surgeon, the urologist, the gynecologist and the thoracic surgeon should have knowledge of and experience in the basic problems common to all patients undergoing major surgical procedures. They should differ only in a superior knowledge of their own fields.

The rapid increase in the number of specialties and their recognition by the approval of new specialty boards have been the source of deep concern to medical educators and leading clinicians, and to the Council on Medical Education and Hospitals of the American Medical Association. Instead of new boards the present tendency is to require certification in the parent board (that of internal medicine or general surgery) and to recognize the specialty as a subsidiary to the Board of Internal Medicine or the Board of

*Adapted from the chapter with the same title in the forthcoming book, *The Physician, His Practice and His Business*, by permission of the publishers, Little, Brown and Company, Boston.

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Surgery. Some of the surgical specialty boards are also gradually increasing the amount of training in general surgery before specialization. However, the harm of overspecialization has been done. Its repair will be slow and difficult.

The specialty boards have two objectives: to establish minimum standards of graduate education and training requirements for physicians who represent themselves to the public as specialists, certifying candidates who have qualified for and successfully passed the board's examination; and to improve the general standards of graduate medical education and the facilities for special training. In both these objectives the boards have been eminently successful.

The American Board of Ophthalmology, created in 1916, was the first specialty certifying board. This was followed by the American Board of Otology in 1924, the American Board of Obstetrics and Gynecology in 1930, and the American Board of Dermatology and Syphilology in 1932. Other specialty groups became increasingly interested in the establishment of their own certifying boards. Each was anxious to take advantage of the experiences of those already formed, but each was also aware of the hazards and dangers that might go along with the spontaneous development of certifying boards, particularly without any real professional sponsorship. Consequently, during 1933 and 1934 the Advisory Board for Medical Specialties was organized and began to function. At the same time the House of Delegates of the American Medical Association passed a resolution authorizing the Council on Medical Education and Hospitals to establish standards of administration for the specialty boards and to give new boards official recognition after they had been passed on and recommended by the Advisory Board.

There are now 18* separate boards listed in the *Directory of Medical Specialists,* with little reason to believe that this number will be increased in the immediate future.

The Directory of Medical Specialists, which had had 6 editions by 1953, lists 43,233 specialists certified before July, 1952. This is a living directory but includes those who may have retired from active practice. It is readily available in libraries, hospitals and physicians' offices. It supplies quick reference by both locality and name. It is to be understood that a directory such as this can only certify that given physicians have fulfilled minimum training requirements and have passed the examinations of their boards. It may well be and frequently is true that in any city or town there are noncertified specialists whose experience and ability may exceed those of others who hold board certification. Most of these are older men who for one reason or another have not considered certification essential particularly since the technical aspects of examination may be trying. Moreover, their formal training is in many cases unacceptable to the boards. With the passage of time, however, there is reason to suppose that this group will gradually disappear, and most of the qualified specialists will hold certification by their individual boards.

*The American Board of Thoracic Surgery is a subsidiary board of the American Board of Surgery.

Specialties and General Practice

Whether or not a physician specializes has a great deal to do with his income, the number of hours he works and where he lives. In general the specialist settles in a larger city, works fewer hours each week and earns more money in a year than the average general practitioner. The work weeks of the specialists in pediatrics and obstetrics, however, are longer than the sixty-one hour week of the general practitioner, and those in general surgery, orthopedic surgery and internal medicine are almost as long. Moreover the income of the general practitioner has increased more rapidly during the past ten years than that of the specialist, and the discrepancy between the two incomes continues to decrease.

To select a specialty rather than general practice on the basis of a shorter work week or higher income would be unrealistic and improper. The demands of those who are sick or have recently undergone operations will continue over weekends and holidays and must be met not only by the general practitioner but frequently by the specialist.

The practice of medicine is not a life of undue sacrifice, nor is it one of high income from a short work week. It is one of devotion to sick people and their families and of responsibility to individuals, to communities, to hospitals and to the profession. Any graduate of a medical school who successfully completes a good graduate training program that prepares him for his particular job, who devotes himself to his work and accepts his full responsibilities either as a specialist or as a general practitioner will be well rewarded financially as well as in the less tangible things in life.

Specialty Training

I have already pointed out the absurd degree to which specialization may be carried and suggested that many specialty programs have neglected training in the fundamental principles of medicine and surgery. This has led to board certification of many whose knowledge beyond that gained in medical school is restricted to a special field of concentration. This early total specialization is contrary to the view of most of those interested in postgraduate medical education, and is difficult to defend in the light of present knowledge of the relation between disease or trauma and the body as a whole.

Increasing recognition of the importance of a good training in general medicine and surgery before specialization in one of the subdivisions of either undoubtedly will greatly influence the specialty boards in determining their future requirements. Therefore,

the recent graduate anticipating a specialty in the clinical branches of medicine should look forward to a thorough training in the problems of general medicine or surgery before getting the special training in one of the subdivisions. This means a minimum of hospital training of four to six years after the year of internship. Hospital training is particularly emphasized here although it is recognized that the number of training programs that accept the young graduate and see him through a complete and carefully integrated program preparing him for board certification are too few. It is the recognition of this fact that has prompted certain certifying boards to accept a portion of training requirements under a preceptor. Experience has shown, however, that few practicing surgeons or physicians can give the young graduate the breadth of experience in emergency work, fractures, urology, thoracic surgery, surgery of the endocrine glands and so on that is available in a large general hospital.

An excellent example of the present concept of board certification in the subspecialties was the recent action of the American Board of Surgery after a request for a board of trauma. With present knowledge of the effect of trauma on the entire organism and with the multiplicity of injuries that occur as the result of modern transportation, a surgeon to be a qualified specialist in trauma must be trained to treat the patient who has had the accident, not just the fractured femur or the ruptured bladder. Therefore, before such an applicant can be certified as a specialist in trauma, he must have demonstrated his training and experience in general surgery by being certified by the American Board of Surgery. Then if his training and experience permit, he could have a subsequent examination in the surgery of trauma and receive a special certificate from the American Board of Surgery, not from a separate board of trauma. This undoubtedly will be the pattern of subsequent specialties in either medicine or surgery.

Introduction to Practice

The transition between resident specialist and practicing specialist may be easy or difficult. Those who complete good qualifying training programs in several of the so-called subclinical specialties, such as radiology, pathology and anesthesiology, have little difficulty in finding attractive openings with excellent remuneration. The demand is still in excess of the supply of good, well trained men. Most of the work is done in hospitals, and one has but to accept a position in an area of need, with a busy practice readily available.

This is not true in many of the other specialties, especially those in which there is a direct responsibility of physician to patient.

Probably the most difficult specialty in which to develop a successful practice is that of major surgery. The patient may be willing to have an x-ray examination or to be given anesthesia or even to be treated medically by a young practitioner. But even in the young man's world of today the average person likes to know a little something of the surgeon who is to perform a serious operation.

The young surgeon fortunate enough to have an association with an older, established, board-certified surgeon, who will be interested in his development, or one who may be asked to join a successful medical group is spared much of the hardship of those who have no such opportunity. To go from a busy surgical residency to the inactive role of a young surgeon just starting his own practice may prove very discouraging.

In a good program every effort is made to give to the resident the best possible training. The emphasis is upon education, not service. Young men in surgery are given the opportunity to make decisions and to do the actual operations (at first under experienced supervision) involving the simpler, less serious procedures. As the experience and technical ability of the surgeon increase he is permitted to do more and more complicated operations until by the time his training is completed he carries, with only a minimum of direct supervision, the responsibility for most of the patients who are admitted to his service. At the end of a good four-year, graded resident program he has become an accomplished surgeon, capable of successfully completing any of the current surgical procedures. Moreover, scarcely a day passes that he does not perform one or more extensive operations. The patients on whom he is operating have come under his care through no effort on his part. They have come to the hospital in which he is working; the members of the visiting staff of the hospital have trained him to do the operations and then have made available to him the patients who need them. As a result of this extended training program an excellent product has been developed. Having acquired this training, however, each must seek his own market. None has been prepared for him.

It is not easy for the young surgeon, who may have spent five or six years after graduation preparing to practice the specialty of his choice, to make the necessary adjustment from the protected life of a resident surgeon to the hazards and trials associated with a competitive practice. Formerly everything possible was done to help him; now every possible resistance may be put in his way — difficulty in obtaining hospital privileges, or the necessity for working under supervision of an established but less competent man. In some areas it may even be suggested that unless he passes to the referring physician a portion of the surgical fee, his services will not be needed. His hospital training did not quite prepare him for these and other problems that he must now face and overcome.

These young men know what they are capable of doing. They do not realize that neither the public nor the potential referring physician shares this knowledge, and that until they have become known locally

and are able to win the confidence and respect of the local community, the opportunities for them to demonstrate their ability will be infrequent. Now when they have the least to do, they must be at their busiest. Always available for emergency calls, interested and active in local hospital, medical-society and community activities, they must in a quiet and efficient manner become a vital part of the community in which they have chosen to live.

To the degree that they know their own training and skills in their specialty, they must have confidence in themselves and in their future. This, together with an untiring interest in their work, an understanding of people and a true desire to co-operate with and whenever possible to be helpful to their new associates cannot but result in the success that is their due.

In the preparation of this article I have called freely on the excellent article, "The Work Week of Physicians in Private Practice," by Howard A. Rusk, M.D., Harold S. Diehl, M.D., Robert W. Barclay and Paul K. Kaetzel, which appeared in the *Journal* on October 22, 1953; and on the study, "The M.D.'s Are Off Their Pedestal," by Herryman Maurer, appearing in the February, 1954, issue of *Fortune*. The authors of both these articles use as the basis of their statistical work the survey carried out jointly by the United States Department of Commerce and the American Medical Association in 1949. In addition I have found very helpful the results of the survey conducted in 1952 by *Medical Economics*.

MEDICAL PROGRESS

INTERMEDIARY METABOLISM (Concluded)*

CLAUDE A. VILLEE, PH.D.†

BOSTON

The synthesis of fatty acids is believed to occur by a reversal of the β oxidation process.[55] Acetyl CoA units are believed to condense, and reduction then occurs at the beta carbon to give the longer chain saturated fatty acid. There is considerable evidence that fatty acids are formed by the condensation of two-carbon units. For example, Hunter and Popjak[56] injected acetate-1-C^{14} ($CH_3C^{14}OOH$) into a lactating goat and collected and analyzed the milk fats. The long-chain fatty acids were isolated and degraded and revealed that there was no C^{14} in positions 2, 4, 6, 8 and so on of the molecule; all the radioactivity was in carbons 1, 3, 5, 7 and so forth; this is evidence that these long-chain fatty acids were synthesized by the condensation of 2-carbon compounds.

Lipogenesis from acetate-1-C^{14} in liver slices is markedly reduced by previous fasting of the animal or a restriction of carbohydrate intake and is enhanced by feeding or by the injection of glucose.[57,58] Lipogenesis is increased by the addition of glucose in vitro and increased further by the addition of glucose as well as insulin. Lipogenesis apparently requires concomitant glycolysis; whether this is needed to supply energy, hydrogen atoms, or in some other capacity is unknown.

Livers become infiltrated with fat when the rate of mobilization of fat to the liver exceeds the rate at which the fats are utilized to form other materials or are oxidized to carbon dioxide and water. It has been known for twenty years that diets deficient in choline will produce a fatty liver. With tracer technics it has been possible to demonstrate that there is a decreased rate of phospholipid synthesis in such livers.[59] Labeled choline has been shown to enter the liver phospholipids,[60] and there is little doubt that choline from the diet is required for the formation of phosphatidyl choline. When phosphatidyl choline (lecithin) synthesis is not occurring at the normal rate fatty acids accumulate as triglycerides; apparently, lecithin plays some part in the early stages of the metabolism of glycerides in the liver. A choline-induced fatty liver can be made normal by the feeding of methionine; the deficiency is apparently one of "labile methyl groups," and the ability of the liver to synthesize choline by transferring methyl groups from methionine to ethanolamine to form choline is unimpaired. The theory that choline is lipotropic because it promotes the mobilization of fatty acids as plasma phospholipids, once very popular, is now doubtful because of the evidence that plasma phospholipids are not a major form of transport of the fatty acids. An alternative hypothesis, that lecithins may be required for the activity of enzymes involved in fatty-acid oxidation, has been advanced.[61] The lecithin may be an integral part of these enzymes, for it appears to be an integral part of other enzymes such as adenosine triphosphatase.

Nucleic Acids

The field of nucleic acid chemistry had been dominated since 1930 by the hypothesis that nucleic acids were tetranucleotides—for example, that desoxyribose nucleic acid (DNA) was composed of equimolar amounts of adenylic, guanylic, cytidylic and thymidylic acids. This implied that all samples of DNA were alike and made it difficult to ascribe biologic specificity to the molecule. With the development of gentle methods of isolating nucleic acids from tissues it became apparent that in nature nucleic acids were

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much larger molecules than tetranucleotides. Since 1946 methods have been developed for separating the constituent nucleotides or bases of nucleic acids by filter-paper chromatography[62] or ion-exchange resins,[63] and making quantitative determinations of these substances by ultraviolet spectrophotometry. Such analyses revealed that DNA isolated from different species had different ratios of their constituent purines and pyrimidines and provided a chemical basis for the biologic specificity of nucleic acids observed. Similar analyses showed that there were differences in the ribose nucleic acids (RNA) isolated from different species, from different organs of the same animal and even from different parts of the cells of a single organ, such as the RNA of the nuclei, mitochondria and soluble proteins of a liver cell.[64]

With the realization that nucleic acids are substances of considerable biologic importance there has been a blossoming of research dealing with their chemistry and metabolism. This has been spurred by a general opinion, based largely on indirect evidence, that nucleic acids play an important part in growth, gene action, protein synthesis and, perhaps, carcinogenesis. It is believed that the specificity of the molecule may be determined by the order and arrangement of the nucleotides, just as the specificity of a protein molecule depends on the order and arrangement of its amino acids. Currently, efforts are being made to develop methods for determining the order of nucleotides in nucleic acids.

It has been found that in a great many species the amount of DNA per cell varies less than any other measurable parameter such as weight or total nitrogen. Somatic cells of mammals have about 3.0×10^{-9} mg. of DNA per cell and germ cells about 1.5×10^{-9} mg. of DNA per cell.[65] Since there is good evidence that the hereditary units, or genes, contain DNA and perhaps that all DNA is contained in the chromosomes, it is understandable that the amount of DNA per cell should be constant. It has been shown that pregnancy or the presence of a tumor increases the amount of DNA and its rate of synthesis as measured by the incorporation of P^{32}, C^{14} glycine or C^{14} formate into DNA in otherwise normal tissues of the body.[66,67] There is at present no explanation for the increase in DNA turnover induced by pregnancy or by tumors in other tissues of the body.

The origins of the components of the purine ring have been determined by Buchanan et al.[47] Previously postulated purine precursors included urea, pyrimidines, arginine and histidine, but experiments with labeled substrates showed that none of these could be the precursor of the purine ring. Buchanan fed C^{13}-labeled precursors to pigeons, isolated uric acid from their excreta, degraded the molecule and determined the amount of label in individual carbon atoms. In this way a new carbon dioxide fixation mechanism was discovered, for carbon 6 of the purine ring was shown to come from carbon dioxide (Fig. 4). Carbons 2 and 8 of the ring were derived from formate. This was one of the first demonstrations of the importance of active 1-carbon compounds in metabolism. Carbons 4 and 5 and nitrogen 7 were shown to come from glycine, incorporated as a unit into the framework of the purine ring.[68] Nitrogens 1, 3 and 9 are derived from ammonia via aspartic or glutamic acid by some mechanism as yet unknown. Other experimenters demonstrated that the same biosynthetic mechanism was operative in yeasts, in mammals and presumably in all types of protoplasm.

An intermediate in the synthesis of purines, 4-amino-5-imidazole carboxamide, has been isolated and

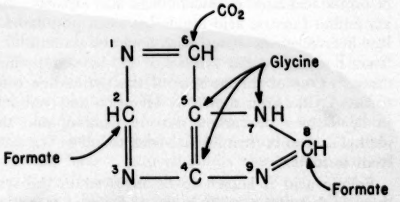

FIGURE 4. *The Purine Ring and Its Metabolic Precursors, Formate, Glycine and Carbon Dioxide.*

identified.[69] Labeled carboxamide has been prepared, injected into rats and shown to result in a labeling of the purines in the tissue nucleic acids.[70] Enzymes in a pigeon-liver extract convert this carboxamide to inosinic acid, a nucleotide. Further experiments by Buchanan and Wilson,[71] using this pigeon-liver extract, indicated that the first step in the conversion of the carboxamide is the addition of ribose and phosphate, followed by a reaction of the riboside phosphate with a formate and folinic acid compound. In this reaction the formate is transferred to the carboxamide riboside, and the purine ring is completed to form inosinic acid. The vitamin, folic acid, has subsequently been shown to have a major role in other reactions involving formate or active 1-carbon compounds such as the conversion of homocysteine to methionine and the interconversions of glycine and serine.[72] Folic acid contains para-aminobenzoic acid in combination with pteridine and glutamic acid, and the previously noted requirements of organisms for p-amino-benzoic acid for growth and purine synthesis are now believed to be for this substance as a precursor of folic acid. The form of folic acid active in 1-carbon metabolism is apparently N-5-formyl-5,6,7,8-tetrahydrofolic acid, or folinic acid.[73,74]

Experiments with a number of different animals have shown that although the purines and pyrimidines of the diet can be used to a slight extent in the synthesis of tissue nucleic acids, most of the nucleic acids are synthesized from small fragments.

Uric acid labeled with N^{15} has been injected into normal and gouty patients to determine the "pool"

of uric acid in each.[75] A normal person has a total body pool of uric acid that amounts to about 1 gm., and its half life is 0.85 days. The pool in a gouty patient may be as much as fifty times as large. Experiments with labeled glycine indicate that gout is characterized by an abnormally large production of uric acid rather than by some impairment in the excretion of this substance.

Less is known about the biosynthesis of the pyrimidine ring. Orotic acid has been suggested as an intermediate in the process, and many experiments have demonstrated that labeled orotic acid is incorporated into tissue nucleic acid pyrimidines by bacteria and mammalian tissue.[76,77] A pathway for the synthesis of orotic acid from oxalacetic acid and aspartic acids via amino fumaric acid amide has been postulated.[78] Rat liver slices incubated with beta and gamma C^{14}-labeled aspartate did synthesize C^{14}-labeled pyrimidines.[79] One of the carbons of the pyrimidine ring, carbon 2, has been shown by Heinrich and Wilson[80] to be derived by carbon dioxide fixation, and the methyl carbon of thymine has been found to originate from formate.[81,82]

Folinic acid is known to be involved in the synthesis of thymine, possibly in the addition of its methyl group.[83] Cobalamin (vitamin B_{12}) functions in the synthesis of the desoxyriboside, thymidine, from thymine, perhaps by some role in the synthesis of desoxyribose itself.[84] Other experiments indicate that vitamin B_{12} is involved in the synthesis of methyl groups and perhaps in other steps in the metabolism of 1-carbon compounds such as the synthesis of serine from glycine.[85]

Several different substances—P^{32}, C^{14}-adenine, C^{14}-formate, N^{15}-adenine, C^{14}-orotic acid and C^{14}-glycine—have been used to measure the rate of renewal of nucleic acids in mammalian tissues. Liver made more efficient use of adenine than of glycine or formate whereas the intestine incorporated glycine or formate more rapidly than adenine itself into tissue nucleic acids. It is clear that no one precursor will give a reliable picture of the relative rates of turnover of the various nucleic acid fractions. The data suggest that there are two, or perhaps more, mechanisms for the synthesis of RNA and that the purine-utilizing system is more efficient in liver and less so in intestine.[86]

There is now fairly good evidence that DNA turns over only in cells capable of dividing. Tissues analyzed from a patient given therapeutic doses of P^{32} showed no incorporation of P^{32} into the DNA of brain, cartilage or skeletal muscle, where mitoses are extremely rare; in contrast considerable amounts of P^{32} were found in the DNA of liver and kidney and even more in that from the lymph nodes and spleen.[87] Experiments in which the rate of incorporation of P^{32}, C^{14}-formate or C^{14}-adenine into tissue DNA was measured also demonstrated a strong correlation with the amount of mitosis observed.[88] The conclusion that the DNA of nondividing cells does not turn over provides a biochemical correlation with the known biologic stability of the gene.

Knight[89] analyzed the nucleic acids present in a number of tobacco-mosaic and cucumber viruses and found that mutant strains have remarkably uniform nucleotide compositions. He suggested that the differences between these strains are due to differences in the amino acid composition of the protein moieties rather than to differences in the nucleic acids.

The biochemical events of virus reproduction have been studied intensively by means of the bacteriophages that attack *Escherichia coli*. From 15 to 40 per cent of the phage DNA may be derived from the bacterial DNA but most of the phosphorus, nitrogen and desoxyribose of the phage nucleic acid is derived from the incubation medium.[90] There is direct evidence that the phage particles are broken down after infection and are partially reutilized in the synthesis of new phage particles.[91] Experiments with doubly labeled purines have shown that the purine ring is transferred intact from the host to the parasite.[92] Since the phage DNA is rich in adenine and the host DNA is rich in guanine, the phage must make relatively more adenine than guanine from other sources.

Steroids

For a number of years, investigators have been adding to knowledge of the metabolism of the various steroids by analyzing the urinary steroid metabolites from normal people, from patients with some sort of endocrine disorder and from patients treated with a variety of endocrines. With improved methods for the detection of small amounts of these materials it has become possible to study some of the details of the intermediary metabolism of the steroids. In addition to experiments dealing with the effects of steroids on tissue metabolism many others have concerned the synthesis, interconversion and degradation of substances having the steroid nucleus.

Rittenberg and Schoenheimer,[93] using deuterium as a label, demonstrated that animal cells can both synthesize and degrade cholesterol and, indeed, that plant sterols are not absorbed through the gut wall, that the cholesterol of the central nervous system is stable and that of the rest of the body is constantly being broken down and synthesized. Fifty per cent of human plasma cholesterol is replaced every eight days.[94]

In vitro experiments show that cholesterol is synthesized by the liver, intestinal mucosa, the adrenal cortex and the walls of arteries and probably by tissues generally. The liver is the primary source of plasma cholesterol. A variety of experiments with labeled substances have indicated that the major and perhaps the sole precursor of cholesterol is acetate.

Bloch[95] and Cornforth et al.[96] studied the synthesis of cholesterol from methyl-labeled and carboxyl-labeled acetate and found that 15 of the 27 carbons of the cholesterol molecule (10 in the ring and 5 in the

side chain) are derived from the methyl carbon of acetate and 12 carbons (9 in the ring and 3 in the side chain) from the carboxyl carbon of acetate. The source of each carbon of the cholesterol molecule was determined, and the distribution of those derived from acetate methyl and carboxyl carbons was such that the molecule could not have been put together by the simple head-to-tail fusion of acetate molecules. The distribution of the labels observed could be explained if cholesterol was synthesized by the condensation of acetate molecules to form acetoacetate (Fig. 3), followed by the decarboxylation of this to acetone and the condensation of acetone and another mol of acetate to yield a 5-carbon acid, which is then reduced to isoprene. The condensation of 6 of these isoprene units would give squalene, a branched polyunsaturated 30 carbon hydrocarbon that was first suggested to be the source of cholesterol by Channon[97] in 1926. Squalene could be converted to cholesterol by the proper folding of the molecule, the formation of cross-linkages, and the deletion of 3 carbon atoms.

Langdon and Bloch[98] fed labeled acetate and unlabeled squalene to a rat and were able to recover labeled squalene from the liver and viscera. When this labeled squalene was fed to mice as much as 10 per cent of the radioactivity was recovered in the tissue cholesterol. The specific activity of the cholesterol was much higher than that in the fatty acids, indicating that the conversion of squalene to cholesterol did not take place via a splitting to 2-carbon units and a synthesis from these. Other experiments with labeled precursors have shown that estrone, testosterone, pregnanediol and cortical steroids are all derived from acetate. It is quite possible that all these are made from cholesterol. When C^{14}-cholesterol is perfused through beef adrenal glands, it is converted to C^{14}-labeled cortical steroids,[99] but this is not proof that cholesterol is an obligatory intermediate in the synthesis of corticoids. The injection of ACTH results in a decrease in the concentration of cholesterol in the adrenal gland of the rat and an increase in the concentration of steroid hormones.[100] This is further evidence that cholesterol is an intermediate in the biosynthesis of steroids.

When beef adrenal cortex is perfused with desoxycorticosterone, it converts this to corticosterone.[101] It therefore has an enzyme to carry on a beta-hydroxylation at position C 11. ACTH is without effect on this process and apparently stimulates steroid production at some earlier step, perhaps before the steroid nucleus is assembled. The beta-hydroxylating enzyme has been isolated from beef adrenal glands and shown to require oxygen, ATP, fumerate, Mg^{++} and DPN as a hydrogen acceptor for its action.

The incorporation of acetate into cholesterol is less in liver slices from fasted rats than in those from fed rats. It is restored to normal if glucose or protein is given. Unlike the situation in fatty-acid synthesis it is also restored to normal by the feeding of fat.[102] Further evidence that the biosynthetic pathways of fatty acids and cholesterol from acetate diverge at an early point comes from experiments with liver slices from diabetic rats.[103] The incorporation of acetate into cholesterol is greater in these slices than in those from normal rats and is reduced by the pretreatment of the rat with insulin. These findings may provide an explanation for the hypercholesterolemia frequently found in diabetic patients and their characteristic tendency to arteriosclerosis. They are consistent with the theory that acetoacetate is the first intermediate in the path from acetate to cholesterol. It is known that acetoacetate production is greatly increased in the diabetic liver as a result of the decreased utilization of acetyl CoA in the Krebs cycle and in fatty-acid synthesis.

The synthesis of steroids involves the formation of active acetate, acetyl CoA, from acetate. Klein[104] showed that CoA-deficient yeasts were unable to synthesize cholesterol. Normal adrenal glands respond in vitro to ACTH with the production of cortical hormones,[105] but the adrenals of pantothenic acid-deficient rats have a reduced ability to synthesize cortical hormones in vitro.[106]

Brady[107] found that the incorporation of labeled acetate into testosterone by testis slices was greatly increased by the addition of chorionic gonadotropin to the incubation medium. Since the hormone did not increase the incorporation of acetate into cholesterol in this system the authors concluded that cholesterol is not an intermediate in the synthesis of testosterone. Samuels and Reich[108] found no effect of chorionic gonadotropin on the enzyme from the testis that oxidizes 3-hydroxysteroids to 3-ketosteroids. It seems that, as in the effect of ACTH on the adrenal gland, the hormone affects the formation of some precursor earlier in the biosynthesis of the steroid.

Hormonal Control of Intermediary Metabolism

A vast amount of research is being done in attempts to understand the mechanism of the regulation of metabolic reactions by hormones. More work has been done with insulin than with any other hormone. There has been a classic controversy over whether the hyperglycemia of diabetes is the result of the underutilization or the overproduction of glucose. Experiments using C^{14}-labeled glucose and rat diaphragm muscle or liver slices have shown that there is underutilization of glucose in both peripheral tissue and liver and an overproduction of glucose in the liver.[109,110] The existence of both underutilization and overproduction in diabetic liver was shown by a series of clever experiments using a variety of C^{14}-labeled substrates.[111]

Some experiments on the disappearance of galactose from the blood of eviscerated, nephrectomized dogs have been interpreted as indicating an action of insulin in promoting the entrance of sugars into

cells.[112] When galactose was injected it reached a constant level in the blood in about ninety minutes. It was calculated that the galactose had been distributed into a volume equal to 45 per cent of the body weight. When insulin was added the blood galactose level dropped. From this new level the investigators calculated that the galactose had been distributed into a volume equal to 70 per cent of the body weight. The inference from these data, that galactose can enter tissue cells only in the presence of insulin, is difficult to accept.

The interpretation of these data—that insulin acts at the plasma membrane to facilitate the transfer of sugars that have a configuration at carbons 1, 2 and 3 similar to glucose—is based on the assumption that galactose, mannose and other sugars tested can be utilized by liver and kidney but not by any other tissue.[112] Wick and Drury[113] found that C^{14}-labeled galactose is metabolized appreciably to carbon dioxide by eviscerated, nephrectomized rabbits. Galactose is thus utilized by peripheral tissue, for the amount metabolized to respiratory carbon dioxide is only a fraction of the total utilized. Experiments in this laboratory[114] show that human placenta utilizes galactose and mannose in vitro at rates that approach those of glucose and fructose.

The report from the Cori laboratory[115] that the enzyme hexokinase in a cell-free system is influenced by the interactions of insulin and other hormones has been confirmed by Reid, Smith and Young[116] but denied by Stadie and Haugaard.[117] The experiments from each laboratory show considerable variability, and the question whether there is or is not an insulin effect and whether hexokinase extracts from diabetic animals differ from those from normal animals seems to depend on interpretations of the statistics of the analytical data.

Insulin has been reported to increase the rate of transfer of phosphate across the cell membrane.[118] The experiments of Rothstein and Larrabee[119] suggest that the enzymes of yeast cells involved in the initial reaction of glucose metabolism are located on the cell surface and can metabolize substrate molecules in the surrounding medium. It is possible that hexokinase is located at the cell surface and that the transfer of glucose across the cell membrane and its phosphorylation are the same process.

There is good evidence that the hexokinase reaction is not the sole site at which insulin affects metabolism. There is a suggestion[120] that the formation of energy-rich phosphate bonds in oxidative phosphorylation is decreased in diabetes and restored to normal by the addition of insulin in vivo or in vitro. Since the mechanism for the production of energy-rich phosphate bonds in oxidation is not understood the role of insulin is obscure. There is evidence that insulin increases the rate of synthesis of lipids and that diabetes is characterized by a severe loss of the ability to synthesize fatty acids. Stetten and Boxer[121] showed that the diabetic rat synthesized only about 5 per cent as much fatty acid from glucose as the normal rat. Lipogenesis from acetate, lactate and pyruvate is also depressed in diabetes. The results from a number of experiments suggest that fatty-acid synthesis requires the simultaneous, unimpaired functioning of the glycolytic system, perhaps for the production and transfer of the energy necessary for synthesis. A similar explanation has been offered for the effects of insulin on protein synthesis observed.[122]

Although the action of insulin on cell-free homogenates or purified enzyme systems has not been proved the effects on the metabolism of intact cells in vitro are clear cut and reproducible. This suggested to Stadie that the intact cell is necessary for hormone action and that the interaction of hormones and enzymes will occur only when cellular morphology is unimpaired. The first step in the action of insulin on any enzyme system of an intact cell must be the entrance of the insulin into the cell and a molecular juxtaposition of the insulin and enzyme molecules. Stadie and his co-workers[123] have shown that insulin does appear to be bound to a variety of tissues. If a section of rat diaphragm is dipped for as short a time as ten seconds into a medium containing insulin, removed and washed exhaustively before being incubated in a glucose medium it exhibits an acceleration of glucose metabolism comparable to a control piece of diaphragm incubated in glucose in addition to insulin. This was interpreted to mean that in the short exposure insulin had been attached to the muscle cells in some strongly bound form and in this form exerted its usual effect on glucose metabolism. When insulin labeled with I^{131} or sulfated with $H_2S^{35}O_4$ was used Stadie and his associates[124] found that the tissue actually concentrated insulin and at equilibrium contained more than the surrounding medium or blood. Muscle tissue was found to contain twice as much insulin as the incubation medium, and leukocytes as much as 100 times more insulin than the surrounding blood.

From these experiments the authors could estimate a quantitative relation between the amount of insulin bound and its biologic activity. This was found to be 3.6 ± 0.76 mg. of extra glycogen synthesized per gram of muscle per hour per microgm. of insulin bound. Or, more clearly, 1 mol of insulin caused the transformation of 13,000 mols of glucose to glycogen per minute above the amount so converted in the absence of insulin. The biologic activity of the bound insulin was found to be the same whether the insulin was injected into the rat before it was killed or derived from a medium in vitro. The full significance of this phenomenon of insulin binding will be clear only when the chemical bonds and cell structures involved have been discovered.

At one time Stadie believed, since tissues from animals previously injected with pituitary or adrenal hormones showed less insulin effect after momentary

exposure to insulin than comparable tissues from uninjected animals, that these hormones competed with insulin for a limited number of specific binding sites on the tissue. With the advent of isotopically labeled insulin it was found that the amount of insulin *bound* was the same in the two cases but that the insulin had less effect because of the contra-insulin action of the injected growth hormone or cortisone. Diaphragms from hypophysectomized rats do not bind any more insulin than those from normal rats, but the bound insulin has a much greater effect in increasing the conversion of glucose to glycogen than comparable amounts of bound insulin in normal tissue.

Summary and Conclusions

This review has attempted to present some of the recent changes in concepts of the pathways of intermediary metabolism. An understanding of these pathways is fundamental to the rational treatment of metabolic disorders such as diabetes mellitus, pernicious anemia, gout and arteriosclerosis. Advances in biochemistry in the past decade have done much to increase understanding of the intimate role of the vitamins and hormones in the body's economy, the vitamins as coenzymes and the hormones as regulators, in some as yet undefined way, of specific enzyme systems.

Although one of the objectives of research on intermediary metabolism is to find ways of treating metabolic abnormalities, it is clear that discovery of the cause of the condition will not necessarily lead to a method of treatment. The cause of the metabolic disorder may be the lack of a hormone, as in diabetes, the lack of a coenzyme, as in pernicious anemia, or the lack of an enzyme. The first two types can be treated by proper replacement therapy, but the third cannot. Glycogen-storage (von Gierke's) disease, phenylketonuria, albinism, alcaptonuria and similar disorders have been shown to be due to the absence or hypofunction of some particular intracellular enzyme. However, there is no known way of introducing the missing enzyme into the cell protoplasm where it is needed even if pure samples of the required enzyme were available. Indeed, even if one could do this, the "cure" would be only temporary, for the evidence of the rapid turnover of cell proteins indicates that the added enzyme would shortly be broken down and not replaced.

The study of the biochemistry of normal and abnormal growth has led to increased understanding of the processes of protein synthesis, nucleic acid metabolism, chemical carcinogenesis, antimetabolites and so on, but the fundamental mechanism of growth and its control is still elusive. The mystery of why cells begin uncontrolled growth is equaled only by that of why most tissues normally stop growing at some given time in development.

The development of technics for separating cell fractions, combined with the refinement of histochemical methods, has led to the realization that the cell has a metabolic as well as a histologic architecture. Certain enzymes and hence certain metabolic steps are localized in the mitochondria or the microsomes or elsewhere.

Perhaps the most important recent advances in biochemistry have been made in the understanding of the release and utilization of energy from foodstuff molecules. It is clear that carbohydrates, fats and proteins are closely interrelated metabolically and that their ultimate oxidative pathway, via the Krebs tricarboxylic acid cycle, is common to all three. In the course of these investigations much has been learned about the synthesis, transformation and utilization of energy-rich phosphate ester and thiol ester bonds.

References

55. Brady, R. O., and Gurin, S. Biosynthesis of fatty acids by cell-free or water-soluble enzyme systems. *J. Biol. Chem.* **199**:421-431, 1952.
56. Hunter, G. D., and Popjak, S. New method for degradation of n-carboxylic acids. *Biochem. J.* **50**:163-168, 1951.
57. Lyon, I., Masri, M. S., and Chaikoff, I. L. Fasting and hepatic lipogenesis from C^{14}-acetate. *J. Biol. Chem.* **196**:25-32, 1952.
58. Medes, G., Thomas, A., and Weinhouse, S. Nutritional factors in fatty acid synthesis by tissue slices *in vitro*. *J. Biol. Chem.* **197**:181-191, 1952.
59. Artom, C., and Swanson, M. A. Incorporation of labeled phosphate into lipids of liver slices. *J. Biol. Chem.* **193**:473-480, 1951.
60. McArthur, C. S., Lucas, C. C., and Best, C. H. Mode of action of lipotropic agents: proof in vivo incorporation of triethyl-β-hydroxyethyl ammonium hydroxide into phospholipid molecule. *Biochem. J.* **41**:613, 1947.
61. Artom, C. Lipid metabolism. *Ann. Rev. Biochem.* **22**:211, 1953.
62. Vischer, E., and Chargaff, E. Separation and quantitative estimation of purines and pyrimidines in minute amounts. *J. Biol. Chem.* **176**:703-734, 1948.
63. Carter, C. E., and Cohn, W. E. Separation of three naturally occurring adenine ribonucleotides by paper chromatography and ion exchange. *Federation Proc.* **8**:190, 1949.
64. Crosbie, G. W., Smellie, R. M., and Davidson, J. N. Phosphorus compounds in cell: composition of cytoplasmic and nuclear ribonucleic acids of liver cell. *Biochem. J.* **54**:287-292, 1953.
65. Mirsky, A. E., and Ris, H. Desoxyribonucleic acid content of animal cells and its evolutionary significance. *J. Gen. Physiol.* **34**:451-462, 1951.
66. Lombardo, M. E., Travers, J. H., and Cerecedo, L. R. Effects of tumors on nucleic acids and their purine constituents in mouse. *J. Biol. Chem.* **195**:43-48, 1952.
67. Payne, A. H., Kelly, L. S., Beach, G., and Jones, H. B. Effects of neoplasia on turnover of nucleic acids studied with formate-C^{14}, and glycine-2-C^{14}. *Cancer Res.* **12**:426-428, 1952.
68. Shemin, D., and Rittenberg, D. On utilization of glycine for uric acid synthesis in man. *J. Biol. Chem.* **167**:875, 1947.
69. Shive, W., Ackermann, W. W., Gordon, M., Getzendaner, M. E., and Eakin, R. E. 5(4)-amino-4(5)-imidazole carboxamide, precursor of purines. *J. Am. Chem. Soc.* **69**:725, 1947.
70. Schulman, M. P., Sonne, J. C., and Buchanan, J. M. Biosynthesis of purines. I. Hypoxanthine formation in pigeon liver homogenates and extracts. *J. Biol. Chem.* **196**:499-512, 1952.
71. Buchanan, J. M., and Wilson, D. W. Studies on biosynthesis of purines and pyrimidines. *Federation Proc.* **11**:534, 1952.
72. Shive, W. B-vitamins involved in single carbon unit metabolism. *Federation Proc.* **12**:639, 1953.
73. Broquist, H. P., Fahrenbach, M. J., Brockman, J. A., Stokstad, E. L. R., and Jukes, T. H. "Citrovorum factor" activity of tetrahydropteroylglutamic acid. *J. Am. Chem. Soc.* **73**:3535, 1951.
74. Pohland, A., Flynn, E. H., Jones, R. G., and Shive, W. Proposed structure for folinic acid-SF, growth factor derived from pteroylglutamic acid. *J. Am. Chem. Soc.* **73**:3247, 1951.
75. Benedict, J. D., Forsham, P. H., and Stetten, DeW., Jr. Metabolism of uric acid in normal and gouty human studied with aid of isotopic uric acid. *J. Biol. Chem.* **181**:183-193, 1949.
76. Weed, L. L., and Wilson, D. W. Incorporation of C^{14}-orotic acid into nucleic acid pyrimidines *in vitro*. *J. Biol. Chem.* **189**:435-442, 1951.
77. Weed, L. L., and Cohen, S. S. Utilization of host pyrimidines in synthesis of bacterial viruses. *J. Biol. Chem.* **192**:699-700, 1951.
78. Mitchell, H. K., and Houlahan, M. B. Investigations on biosynthesis of pyrimidine nucleosides in *Neurospora*. *Federation Proc.* **6**:506, 1947.
79. Lagerkvist, U., Reichard, P., and Ehrensvärd, G. Aspartic acid as precursor for ribonucleic acid pyrimidine. *Acta chem. Scandinav.* **5**:1212, 1951.
80. Heinrich, M. R., and Wilson, D. W. Biosynthesis of nucleic acid components studied with C^{14}. I. Purines and pyrimidines in rat. *J. Biol. Chem.* **186**:447-460, 1950.
81. Totter, J. R., Volkin, E., and Carter, C. E. Incorporation of isotopic formate into nucleotides of ribo- and desoxyribonucleic acids. *J. Am. Chem. Soc.* **73**:1521, 1951.
82. Elwyn, D., and Sprinson, D. B. Extensive synthesis of methyl group of thymine in adult rat. *J. Am. Chem. Soc.* **72**:3317, 1950.
83. Shive, W. Utilization of antimetabolites in study of biochemical processes in living organisms. *Ann. New York Acad. Sc.* **52**:1212-1234, 1950.

84. Shive, W., Ravel, J. M., and Harding, W. M. Interrelationship of purines and vitamin B_{12}. *J. Biol. Chem.* **176**:991, 1948.
85. Stekol, J. A., Weiss, S., and Weiss, K. W. Vitamin B_{12} and folic acid in synthesis of choline in rat. *Arch. Biochem.* **36**:5-10, 1952.
86. Drochmans, P., Marrian, D. H., and Brown, G. B. Incorporation of formate into pentosenucleic acids in various organs of rat. *Arch. Biochem.* **39**:310, 1952.
87. Osgood, E. E., et al. Relative rates of formation of new leukocytes in patients with acute and chronic leukemias: measured by uptake of radioactive phosphorus in isolated desoxyribosenucleic acid. *Cancer* **5**:331-335, 1952.
88. Furst, S. S., and Brown, G. B. On role of glycine and adenine as precursors of nucleic acid purines. *J. Biol. Chem.* **191**:239-247, 1951.
89. Knight, C. A. Nucleic acids of some strains of tobacco mosaic virus. *J. Biol. Chem.* **197**:241-249, 1952.
90. Kozloff, L. M., Knowlton, K., Putnam, F. W., and Evans, E. A., Jr. Biochemical studies of virus reproduction. V. Origin of bacteriophage nitrogen. *J. Biol. Chem.* **188**:101-116, 1951.
91. Kozloff, L. M. Biochemical studies of virus reproduction. VII. Appearance of parent nitrogen and phosphorus in progeny. *J. Biol. Chem.* **194**:95-108, 1952.
92. Koch, A. L., Putnam, F. W., and Evans, E. A., Jr. Purine metabolism of *Escherichia coli*. *J. Biol. Chem.* **197**:105-112, 1952.
93. Rittenberg, D., and Schoenheimer, R. Deuterium as indicator in study of intermediary metabolism. XI. Further studies on biological uptake of deuterium into organic substances, with special reference to fat and cholesterol formation. *J. Biol. Chem.* **121**: 235-253, 1937.
94. London, I. M., and Rittenberg, D. Deuterium studies in normal man. I. Rate of synthesis of serum cholesterol. II. Measurement of total body water and water absorption. *J. Biol. Chem.* **184**:687-691. 1950.
95. Bloch, K. Biological synthesis of cholesterol. *Recent Progr. Hormone Research* **6**:111, 1951.
96. Cornforth, J. W., Hunter, G. D., and Popjak, G. Distribution of acetate carbon in ring structure of cholesterol. *Biochem. J. (Proc. Biochem. Soc.)* **53**:xxxiv, 1953.
97. Channon, H. J. Biological significance of unsaponifiable matter of oils: experiments with unsaturated hydrocarbon, squalene (spinacene). *Biochem. J.* **20**:400-408, 1926.
98. Langdon, R. C., and Bloch, K. Biosynthesis of squalene and cholesterol. *J. Am. Chem. Soc.* **74**:1869, 1952.
99. Zaffaroni, A., Hechter, O., and Pincus, G. Conversion of C^{14} labeled acetate and cholesterol to adrenocortical hormones by perfused adrenal glands. *Federation Proc.* **10**:150, 1951.
100. Haines, W. J., Nielson, E. D., Drake, N. A., and Woods, O. R. Biosynthesis of 17-alpha-hydroxycorticosterone from acetate. *Arch. Biochem.* **32**:218-220, 1951.
101. Hayano, M., Dorfman, R. I., and Yamada, E. Y. Conversion of desoxycorticosterone to glycogenic material by adrenal homogenates. *J. Biol. Chem.* **193**:175-181, 1951.
102. Tomkins, G. M., and Chaikoff, I. L. Cholesterol synthesis by liver. I. Influence of fasting and of diet. *J. Biol. Chem.* **196**: 569-573, 1952.
103. Hotta, S., and Chaikoff, I. L. Cholesterol synthesis from acetate in diabetic liver. *J. Biol. Chem.* **198**:895-899, 1952.
104. Klein, H. P. Relation of coenzyme A to steroid and total lipid synthesis in yeast. *Federation Proc.* **10**:209, 1951.
105. Saffran, M., Grad, B., and Bayliss, M. J. Production of corticoids by rat adrenals *in vitro*. *Endocrinology* **50**:639-643, 1952.
106. Soltes, M., and Villee, C. A. Unpublished data.
107. Brady, R. O. Biosynthesis of radioactive testosterone in vitro. *J. Biol. Chem.* **193**:145-148, 1951.
108. Samuels, L. T., and Reich, H. Chemistry and metabolism of steroids. *Ann. Rev. Biochem.* **21**:129-178, 1952.
109. Villee, C. A., and Hastings, A. B. Metabolism of C^{14}-labeled glucose by rat diaphragm *in vitro*. *J. Biol. Chem.* **179**:673-687, 1949.
110. Hastings, A. B., Teng, C.-T., Nesbett, F. B., and Sinex, F. M. Studies on carbohydrate metabolism in rat liver slices. I. Effect of cations in media. *J. Biol. Chem.* **194**:69-81, 1952.
111. Renold, A. E., Teng, C.-T., Nesbett, F. B., and Hastings, A. B. Studies on carbohydrate metabolism in rat liver slices. II. Effect of fasting and of hormonal deficiencies. *J. Biol. Chem.* **204**:533-546, 1953.
112. Levine, R., Goldstein, M. S., Huddlestun, B., and Klein, S. P. Action of insulin on permeability of cells to free hexoses as studied by its effect on distribution of galactose. *Am. J. Physiol.* **163**: 70-76, 1950.
113. Wick, A. N., and Drury, D. R. Action of insulin on volume of distribution of galactose in body. *Am. J. Physiol.* **173**:229-232, 1953.
114. Lust, J. E., and Villee, C. A. Unpublished data.
115. Price, W. H., Cori, C. F., and Colowick, S. P. Effect of anterior pituitary extract and of insulin on hexokinase reaction. *J. Biol. Chem.* **169**:633, 1945.
116. Reid, E., Smith, R. H., and Young, F. G. Hexokinase-inhibiting activity of diabetogenic pituitary extracts. *Biochem. J. (Proc. Biochem. Soc.)* **42**:xix, 1948.
117. Stadie, W. C., and Haugaard, N. Hexokinase reaction in tissue extracts from normal and diabetic rats. *J. Biol. Chem.* **177**:311-324, 1949.
118. Sacks, J. Mechanism of phosphate transfer across cell membranes. *Cold Spring Harbor Symposia Quant. Biol.* **13**:180, 1948.
119. Rothstein, A., and Larrabee, C. Relationship of cell surface to metabolism. II. Cell surface of yeast as site of inhibition of glucose metabolism by uranium. *J. Cell. & Comp. Physiol.* **32**:247-259, 1948.
120. Goranson, E. S., and Erulkar, S. D. Effect of insulin on aerobic phosphorylation of creatine in tissues from alloxan-diabetic rats. *Arch. Biochem.* **24**:40-48, 1949.
121. Stetten, DeW., Jr., and Boxer, G. E. Studies in carbohydrate metabolism. III. Metabolic defects in alloxan diabetes. *J. Biol. Chem.* **156**:271-278, 1944.
122. Krahl, M. E. Effect of insulin and pituitary hormones on glucose uptake in muscle. *Ann. New York Acad. Sc.* **54**:649-670, 1951.
123. Stadie, W. C., Haugaard, N., Marsh, J. B., and Hills, A. G. Chemical combination of insulin with muscle (diaphragm) of normal rat. *Am. J. M. Sc.* **218**:265-274, 1949.
124. Stadie, W. C., Haugaard, N., and Vaughan, M. Studies of insulin binding with isotopically labeled insulin. *J. Biol. Chem.* **199**: 729-739, 1952.

MEDICAL INTELLIGENCE

USE OF ERYTHROMYCIN IN DIPHTHERIA

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THE aim of treatment of diphtheria is neutralization of the toxin and elimination of bacteria from the throat. The purpose of this communication is to report on the rapid bactericidal activity of erythromycin and its usefulness in the treatment of clinical diphtheria.

Diphtheria antitoxin, since its introduction about 1895, has been strikingly effective in neutralizing the exotoxin elaborated by *Corynebacterium diphtheriae*. However, toxin continues to be produced until the bacteria themselves cease to multiply. An effective agent that quickly eliminates the organisms from the nose and throat is greatly to be desired.

All the available antibiotics, both locally and systemically, have some bactericidal effect on the organisms. The bacteria persist in the throat an average of thirty-three days in patients treated with antitoxin alone. Penicillin, chlortetracycline and oxytetracycline eliminate the bacteria from the throat in three or four days. No observable difference in the clinical course was noted in acute cases treated with antitoxin and penicillin and those treated with antitoxin alone.†

The low incidence of acute diphtheria in this community at present offers real difficulty in the evaluation of newer therapeutic agents. However, from April to November, 1953, erythromycin‡ was administered to 3 patients with acute pharyngeal diphtheria and to 1 diphtheria carrier. In all 4 patients the organisms were cleared from the nose and throat within

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†Weinstein, L. Treatment of acute diphtheria and chronic carrier state with penicillin. *Am. J. M. Sc.* **213**:308-314, 1947.

‡Ilotycin, kindly supplied by Dr. J. W. Smith, of Lilly Research Laboratories, Indianapolis, Indiana.

twenty-four hours, and repeated cultures were negative for *C. diphtheriae* during the period of hospitalization. Two patients with acute disease received antitoxin in addition to erythromycin. The patient with the mild case and the diphtheria carrier were treated with erythromycin alone. The observation period after cessation of treatment varied from one to three weeks. Cultures were taken daily and planted on Loeffler's medium. Virulence studies were performed on the original isolation culture, and all 4 patients were found to be harboring organisms that proved to be virulent on guinea-pig inoculation. Repeated urinalyses and morphologic examinations of the blood revealed no significant abnormality.

Case Reports

Case 1. R.S. (F.R.G.H.9499), a 50-year-old housewife, noticed a sore throat 3 days before admission to the hospital. On the day of admission throat cultures demonstrated *C. diphtheriae*. There was a typical patchy, grayish-white membrane over the uvula, pharynx and both tonsillar areas. She had been immunized against diphtheria about 20 years previously. She was given 1200 mg. of erythromycin daily in 3 divided doses for 5 days. Throat cultures were negative for *C. diphtheriae* on the day after the beginning of erythromycin therapy and continued negative during the remainder of the hospital stay, and for 7 days of follow-up study.

Case 2. M.K. (F.R.G.H. 9496),* a 4-year-old boy, complained of a sore throat, on the day before admission. On admission he seemed a little better, but a heavy yellow membrane was noted over both tonsils. Cultures were positive for *C. diphtheriae*. He had been immunized with diphtheria-tetanus-pertussis vaccine at the age of 6 months, and a booster dose had been administered at the age of 1 year. In the hospital he received 50,000 units of diphtheria antitoxin on admission and an additional 60,000 units on the following day. He was given 600 mg. of erythromycin daily in 3 divided doses for 1 week. On the day after the start of erythromycin therapy throat cultures became persistently negative for *C. diphtheriae*, remaining so for an additional 5 days.

Case 3. G. L. (F.R.G.H. 9465),* a 4-year-old girl, had a sore throat for 3 days before admission. On the morning of admission severe respiratory difficulty developed. The throat was edematous, and a dirty-gray membrane extended over both tonsillar areas and the uvula. There was a serosanguineous discharge from the left nostril, as well as enlarged and tender cervical lymph nodes bilaterally. She had never been immunized against diphtheria. A throat culture revealed *C. diphtheriae*. She was given 125,000 units of diphtheria antitoxin on arrival at the hospital. Because of inability to swallow an intravenous preparation of erythromycin was obtained, and 500 mg. was administered daily in 2 doses for 5 days. By this time she was able to swallow and the erythromycin was continued in a daily amount of 600 mg. by mouth for an additional 5 days. After the original positive throat culture all cultures were negative during the entire stay of 1 month in the hospital as well as the follow-up period of 3 weeks.

*Referred through the courtesy of Dr. John E. Manning, of Fall River.

Case 4. (F.R.G.H. 9466), a 9-year-old boy (the brother of Case 3), was admitted to the hospital because of a positive throat culture for *C. diphtheriae* discovered during the course of an epidemiologic survey of the family. He had been immunized with diphtheria toxoid at the age of 5. Examination of his throat revealed only diffuse redness. There was no membrane. Several more positive cultures for *C. diphtheriae* were obtained before treatment with erythromycin was started. He was then given 800 mg. of erythromycin daily by mouth in 4 divided doses for 6 days. Twenty-four hours after the beginning of this therapy, all cultures were negative for *C. diphtheriae;* cultures remained negative during a 10-day follow-up study.

Discussion

Three of these patients received the erythromycin by mouth. The fourth required intravenous administration. This was given in an amount of 250 mg. twice daily until a total of 2.25 gm. had been given. Each 250-mg. dose was diluted in 250 cc. of physiologic saline solution or in the same amount of 5 per cent glucose in water and given intravenously over a period of ninety minutes. An unexplained finding is the observation that when the glucose in water was used vomiting occurred, but there were no gastrointestinal disturbances when the erythromycin was diluted with 250 cc. of saline solution. The same vein was utilized over the five-day period without any evidence of phlebitis or thrombosis. Intermittent venipunctures, rather than the use of an indwelling catheter, were decided on since it was thought that excessive amounts of fluid would be required to maintain patency of the catheter. As it was, moderate peripheral edema developed, presumably from the large amount of sodium chloride given. Within twenty-four hours throat cultures became negative for *C. diphtheriae* and remained so. In forty-eight hours marked lessening of toxicity was observed.

Conclusions

Erythromycin appears to be effective in rapidly clearing diphtheria organisms from the throat.

In addition to its use in acute cases, it was helpful in eliminating diphtheria bacilli in 1 carrier.

The availability of an intravenous preparation increases its usefulness in the very sick patient.

Erythromycin is advocated as an adjunct and not as a substitute for antitoxin in acute diphtheria.

465 Walnut Street

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40271

PRESENTATION OF CASE

A seventy-year-old retired rubber worker entered the hospital because of pain in the right side of the chest.

About three months previously severe pain on the right side of the chest that disappeared in one day developed. An x-ray examination was advised but was refused. Thereafter, the patient was entirely free of pain until four days before admission, when the pain recurred and persisted; it was pleuritic and involved the right lower part of the chest and the upper portion of the abdomen. For the past month and a half he had also had mild ankle swelling, for which he had been digitalized. The weight had decreased from 190 to 133 pounds during the previous year. There was no history of fever, cough, hemoptysis, expectoration or jaundice.

Twelve years before admission he had had left-sided renal colic, and a stone was removed from the left ureter. A year later he had fallen down twenty steps and was unconscious for ten hours; however, x-ray examination did not reveal a fracture of the skull. Four years before admission episodes of dizziness, slight motor weakness and a positive Babinski sign on the right side had been diagnosed as cerebral thrombosis; the blood pressure was 180 systolic, 100 diastolic. In the past year he had received electric-shock therapy for paranoid delusions and hypochondriac complaints. For some years he had been drinking up to half a gallon of wine a day.

Physical examination revealed a chronically ill, thin man lying on his right side and breathing rapidly and shallowly. There was no cyanosis or jaundice. The neck veins were distended 4 cm. above the clavicles in the upright position. The right side of the chest was splinted, and over its lower half there were friction rubs, dullness and diminished breath sounds and tactile fremitus. There were no rales. The left side of the chest was clear. The heart was slightly enlarged, and there was a Grade 2 systolic murmur at the apex. The liver edge was felt 2 fingerbreadths below the right costal margin and was slightly tender. The other abdominal organs were not palpable. There was + + edema of the legs, more noticeable on the left. The knee and ankle jerks were active and equal. The right plantar reflex was upward, and the left downward.

The temperature was 98.6°F., the pulse 140, and the respirations 32. The blood pressure was 130 systolic, 70 diastolic.

The urine had a specific gravity of 1.020 and gave a + + test for albumin; the sediment contained many red cells, 3 to 5 white cells and a rare granular cast per high-power field. Two subsequent urinalyses were negative except that one showed 5 red cells per high-power field in the sediment. A urine culture grew out rare colonies of *Staphylococcus albus*. The urinary urobilinogen was 1.5 Ehrlich units and, one week later, 0.39 Ehrlich units. Examination of the blood showed a hemoglobin of 14 gm. per 100 cc. and a white-cell count of 9000, with a normal differential. The prothrombin time was 13 seconds (normal, 14 seconds). The serum bilirubin was 0.8 mg. direct, 1.6 mg. total, the nonprotein nitrogen 60 mg., the calcium 9.2 mg., the phosphorus 3.9 mg., the alkaline phosphatase 4.7 units, the total protein 6.2 gm., the albumin 2.8 gm., and the globulin 3.4 gm. per 100 cc. Cephalin flocculation was + + + in twenty-four and forty-eight hours. One blood culture was negative. Stool examinations were repeatedly negative for blood, for ova and for parasites, and culture revealed no pathogenic organisms. An electrocardiogram demonstrated a normal sinus rhythm, low T waves in standard and limb leads and in Leads V_4, V_5 and V_6, and low R waves in Leads V_1 and V_2 and in Leads V_1 through V_6 only RS complexes were recorded. The tracing was suggestive of a marked clockwise rotation of the heart. A roentgenogram of the chest disclosed fluid in the right pleural cavity up to the eighth interspace. On fluoroscopic examination the right leaf of the diaphragm was elevated and moved poorly; a rectangular area of density seen just above it posteriorly had the appearance of atelectasis. A film of the abdomen revealed diffuse haziness, with possibly a small amount of fluid. The liver was large; the spleen was questionably so. In an intravenous pyelogram there was delayed and insufficient excretion from the kidneys. Sigmoidoscopic examination was negative. A chest tap yielded 25 cc. of clear, yellow-pink material containing 10,000 red cells and 600 white cells per cubic millimeter, with a total protein of 1.6 gm. per 100 cc. and 100 cc. of grossly bloody fluid. Cytologic examination was unsatisfactory.

The patient was treated with analgesics, digitoxin and Dicumarol. The temperature curve was persistently irregular, with elevations to 100°F. He con-

tinued to be weak and anorectic and lost 10 pounds of weight in one week. The liver was hard and increased in size, gradually extending to 10 cm. below the right costal margin. On the eleventh hospital day the same examiner was able to palpate a round, grapefruit-sized, smooth and firm mass in the right upper quadrant toward the midline that could not be separated from the liver.

During the next two days several examiners believed the mass had decreased in size. The patient's condition remained unchanged and on the fifteenth hospital day an operation was performed.

Differential Diagnosis

Dr. Myles P. Baker*: This problem seems to center on the nature of the hepatic enlargement and particularly on the mass that appeared immediately before operation. In an elderly man who had been losing strength fast, the facts in the present illness that seem to me of most importance are precipitous weight loss over a period of a year, the development of ankle edema in six weeks and the acute pleuritic pain on the right side. The past history included two or three episodes that probably did not have much relation to the chief problem presented here—namely, the stone in the left ureter, the cerebral concussions and the cerebrovascular accident. The history of possibly more than mild alcoholism and the suggestion that in the past year this seventy-year-old man had been behaving strangely may have had something to do with the present troubles. The important findings on physical examination were, besides the obvious, acute pain in the right side of the chest and splinting on that side, the distention of the neck veins, which in a thin person may not be of telling significance, the large or low and slightly tender liver and the edema. I doubt if the right plantar response had much to do with the present trouble. May we see the x-ray films?

Dr. John F. Gibbons: The chest films show the fluid in the right pleural cavity and an area of density behind the heart in the lateral projection that could be due to some degree of atelectasis. The heart is not particularly enlarged; there is no evidence of pulmonary vascular congestion and nothing else abnormal in the lungs. In a film of the abdomen the liver appears to be enlarged; the spleen cannot be outlined very well, but I do not think it is enlarged. I do not see any mass in the right upper quadrant or in the epigastrium. In a film of the pyelogram made twenty minutes after the injection of dye the collecting systems are only faintly visualized, indicating some impairment of renal excretion. The kidneys are normal in size and shape, and again there is no evidence of an abnormal soft-tissue mass on these films.

Dr. Baker: The x-ray films exclude renal stone?

Dr. Gibbons: Yes.

*Physician, Massachusetts General Hospital.

Dr. Baker: They are not too decisive in excluding some obstruction to the left renal pelvis.

Dr. Gibbons: I think that is excluded because the collecting system is completely although faintly outlined and is not dilated. There is some dye in the bladder by this time.

Dr. Baker: And the right leaf of the diaphragm is certainly high.

Dr. Gibbons: Yes; it is.

Dr. Baker: But not domed.

Dr. Gibbons: No; the entire roof of the diaphragm is elevated.

Dr. Baker: Is there evidence of congestive heart failure?

Dr. Gibbons: There is none that I can see.

Dr. Baker: The absence of rales at the right base is perhaps a point to be taken as casting doubt on congestive heart failure as an important contributory factor in this man's leg edema. There was no mention of whether he was orthopneic or continued to be dyspneic even when the pleuritic pain was relieved. The laboratory tests give us a certain amount of information: the microscopic hematuria is a striking finding even though its presence was not confirmed except on one or two subsequent specimens. The patient was able to concentrate the urine to 1.020 so that some other factor, such as dehydration, may well have contributed to the one nonprotein nitrogen determination of 60 mg. per 100 cc. I doubt if I am dealing with any renal lesion causing renal insufficiency. The absence of anemia is noteworthy. The liver-function tests showed the blood bilirubin and likewise the alkaline phosphatase level to be slightly elevated. There was a definitely abnormal cephalin flocculation and an inversion of the albumin-globulin ratio that I think may have been important in this case. To go back to the heart for a moment, the electrocardiographic evidence I take as important only because it was not typical of a chronic cor pulmonale.

As far as this man's progress in the ten or eleven days that he spent on the ward is concerned, I think the important development is the enlargement of the liver. The liver was definitely hard, and a mass inseparable from it had developed in the right epigastrium. It seems to me that this course of events points to three conclusions: that congestive heart failure was not primarily the cause of the edema; that the large, somewhat tender liver was probably not a contributory factor to the acute right-sided chest pain; and that, more probably, some malignant process involved the liver. The development of acute right-sided pleuritic pain raises, of course, the old diagnostic questions of infection, infarction or cancer. I should think that, because of its suddenness of onset and the absence of other signs of infection and with the warning signal three months before admission, pulmonary embolization, infarction and subsequently accumulation of bloody fluid were highly likely as a

complication of some other disease that involved the liver.

What are the possibilities of diagnosis in a man of seventy, who was too sick to have an x-ray examination of the gastrointestinal tract to exclude a primary focus for a malignant lesion? Several stools were tested for occult blood, and none were positive, so that one turns from the possibility of cancer of the stomach or colon to cancer of the pancreas or primary hepatoma associated with latent cirrhosis of the liver. We know that with cancer of the body of the pancreas thromboembolic disease is not uncommon and is often a predominant factor symptomatically speaking. That the patient was only barely jaundiced is not a factor against cancer of the pancreas with metastases to the liver; probably 75 per cent of patients with cancer of the body and tail of the pancreas are not jaundiced. The absence of pain in the upper part of the abdomen is certainly unusual if he had cancer of the pancreas. The same reservation holds for the possibility that the enlarging liver was due to hepatoma. Most of those patients also have pain in the upper part of the abdomen. One bit of data given in the laboratory tests is in favor of a latent cirrhosis of the liver—the inverted albumin-globulin ratio. That, I think, would be unexpected in a man who had simply been malnourished during the last few months of his life. The last patient that I saw with cancer of the body of the pancreas, with liver metastases, had a slightly low serum albumin but no increase in the serum globulin during the last month; in fact the albumin-globulin ratio was just exactly the reverse of this man's. The hematuria probably had nothing to do with this man's death, and I doubt that, if he had a malignant lesion, it involved the kidneys. Perhaps the hematuria was not explained at all. The edema of the ankles before admission was probably due either to the combination of low serum albumin and impending congestive heart failure or to retroperitoneal cancer.

My first choices, then, for the explanation of this man's rapidly enlarging liver and precipitous downhill course are hepatoma superimposed on cirrhosis of the liver, and pulmonary embolization and infarction. I doubt if any evidence of heart disease, besides an aging heart, and any explanation of the hematuria were found. My second choice is cancer of the pancreas, with extensive liver metastases and possibly a hemorrhage into the liver as an explanation for the developing mass. I assume that the operation was a liver biopsy, which I have found useful in making the diagnosis of metastatic cancer of the liver without the necessity of exploration.

DR. DANIEL S. ELLIS: When I saw this patient I was disturbed by the sudden appearance of the grapefruit-sized mass in a period of forty-eight hours. I believed that if this observation was correct a large hematoma of the liver had to be considered, possibly secondary to infarction of the liver or secondary to bleeding in a necrotic tumor. If one could discount the statement that the mass had appeared suddenly, I believed, as Dr. Baker did, that the most likely diagnosis was cirrhosis, with superimposed hepatoma of the liver. I thought that the patient should be biopsied and did do a liver biopsy on him.

DR. EDWARD F. BLAND: Did Dr. Ellis think the lung lesion was an ordinary infarct, or did he think it was a tumor infarct?

DR. ELLIS: I apparently did not commit myself about the lung lesion. When I saw the x-ray film a minute ago I wondered if it was not tumor. Dr. Gibbons did not give it much consideration so that I have talked myself into agreeing with Dr. Baker that it was infarction rather than tumor.

CLINICAL DIAGNOSIS

?Hematoma of liver, secondary to infarction of tumor.

?Hepatoma superimposed on cirrhosis.

DR. MYLES P. BAKER'S DIAGNOSIS

Hepatoma, with superimposed cirrhosis of liver.

ANATOMICAL DIAGNOSIS

Hepatoma.

PATHOLOGICAL DISCUSSION

DR. WINFIELD S. MORGAN: Dr. Baker was correct on both counts: the operation was a needle biopsy of the mass in the right epigastrium, and this showed a hepatoma consisting of large cells arranged in columns and solid masses resembling the parenchymatous cells of the liver. Unfortunately, no non-neoplastic liver parenchyma was included in the specimen so we have no clear idea of the exact nature of any underlying hepatic disease.

DR. ELLIS: Do you know what was present in the lung?

DR. MORGAN: No; we do not. The patient died within a few days of the biopsy, but unfortunately no autopsy was permitted.

DR. BAKER: Is it not true that distant metastases in hepatoma are decidedly unusual? Is that not in favor of thromboembolic disease?

DR. MORGAN: I am afraid we shall never know the nature of the pulmonary lesion, Dr. Baker. Although it is true that we do not see metastases from a hepatoma as widespread as those from other carcinomas, the most common site of metastasis is the lung, and we have seen metastases to the spine.

CASE 40272

PRESENTATION OF CASE

An eighty-year-old Italian widow was referred to the hospital because of pain in the flank.

The patient was unable to speak English, but a history was supplied by her relatives. She had been in fairly good health until two days before admission, when she began to refuse food and drink. On the next day she complained of severe costovertebral-angle pain on the left, and that night she noted gross hematuria. The pain persisted unabated from the time of onset to admission to the hospital. She had not had any nausea or vomiting, except on the evening before admission after she had taken some castor oil. There had never been any chest pain, chills or fever. She had been constipated for many years, but had had no diarrhea, melena or bleeding. She had had nocturia for many years, but no burning on urination. No gross hematuria had ever been noted until the present episode.

The patient had been under the care of her family physician for six months before admission because of nightly paroxysmal dyspnea, exertional dyspnea and palpitations, and had been taking digitoxin and vitamins. Nineteen years before admission she had allegedly received irradiation of the uterus, but no further details were known concerning this.

Physical examination revealed an apprehensive, rather emaciated, chronically ill looking woman. She had a frequent, dry cough and audible expiratory wheezes. The neck veins were distended up to 7 cm. when the patient sat in a 90° position. There was a moderate dorsal kyphosis. The percussion note of the chest was resonant. There were fine, moist inspiratory rales and expiratory wheezes throughout the lower half of each side of the chest. The apical impulse was diffuse in the midaxillary line. There was a harsh, Grade 3 apical systolic murmur. The pulmonic second sound was louder than the aortic. The abdomen was moderately distended and tympanitic. An occasional tinkle was heard on auscultation. There was slight tenderness in the left costovertebral angle and left flank. Liver dullness was percussed 7 cm. below the right costal arch, but the edge was not felt. There was a large cystocele and rectocele. The cervix was absent. No masses were felt in the pelvis. There was ++++ pitting edema of both ankles.

The temperature was 99°F., the pulse 90 and regular, and the respirations 28. The blood pressure was 170 systolic, 90 diastolic.

The urine had a specific gravity of 1.020, with a trace of albumin, and the sediment contained 50 to 100 white cells and 20 to 50 red cells per high-power field. A urine culture disclosed rare colonies of *Escherichia coli;* no organisms were seen on the smear. Examination of the blood demonstrated a hemoglobin of 12 gm. per 100 cc. and a white-cell count of 22,800, with 92 per cent neutrophils. The total protein was 6.5 gm. with an albumin-globulin ratio of 1.8. The sodium was 136 milliequiv, the potassium 3.0 milliequiv., the chloride 87 milliequiv. and the carbon dioxide 36 milliequiv. per liter. The nonprotein nitrogen was 44 mg. per 100 cc. The prothrombin time was 14 seconds (normal, 13 seconds). An electrocardiogram showed a PR interval of 0.16 second and a QRS interval of 0.07 second. The rate was 96. There was a sinus rhythm, with atrial and ventricular premature systoles. The R waves were tall in Leads 1, aVL, V_4, V_5 and V_6 and the T waves inverted in Leads 1, aVL, V_5 and V_6. An x-ray film of the chest revealed enlarged hilar shadows and engorgement of the pulmonary vessels. The heart was enlarged, chiefly in the region of the left ventricle. The cardiothoracic ratio was 15.5:24.5. The aorta was tortuous, and the arch calcified. A plain film of the abdomen suggested the presence of fluid, although this was not definite. The right kidney appeared to be of normal size, shape and position. The left kidney was not well visualized. No calculi were seen. An intravenous pyelogram disclosed normal calyxes, pelvis and ureter; the dye was promptly excreted from the right kidney in satisfactory concentration. The right kidney was of normal size and shape, although slightly lower than usual. The left kidney was not seen. The bladder was not satisfactorily visualized because the dye was diluted by urine, which filled the bladder from the beginning of the examination. Cystoscopic examination demonstrated slight chronic cystitis. A left retrograde pyelogram indicated a normal left ureter, which entered a dilated pelvis (Fig. 1). The kidney was rotated on its axis and showed marked hydronephrosis. A smooth area was noted on the inferior and lateral calyxes and was interpreted as "questionable pressure effect." The lower calyx appeared blunted. The upper outer calyx failed to fill. No definite masses were seen although there was a suggestion of a mass encroaching on the renal pelvis. Culture of the urine from the left kidney revealed no growth. A barium-enema examination disclosed mul-

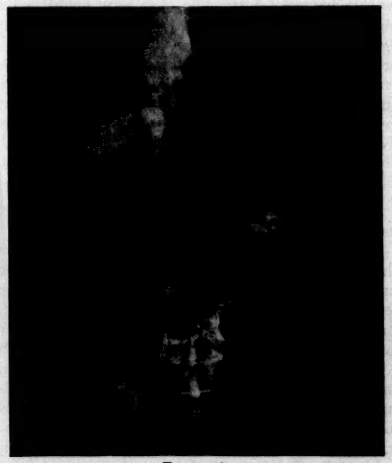

FIGURE 1.

tiple small diverticula in the rectosigmoid and was otherwise negative.

During the next seven days the patient was treated with a cardiac regimen. She showed much improvement, with amelioration of dyspnea, clearing of the lungs and peripheral edema. On the eighth hospital day pain in the left flank and over the left precordium followed withdrawal of blood from the arm and lasted for five minutes. There was no nausea or vomiting although she was allegedly cyanotic during the episode. She stated that she had had similar pains in the past after exacerbations of the flank pain. The blood pressure was 140 systolic, 80 diastolic, the pulse 90, and the respirations 24. Examination of the heart was unchanged. A few fine rales were heard in the lung bases. Examination of the abdomen showed a "greatly enlarged, freely movable, smooth left kidney." The legs were nontender. An electrocardiogram revealed no significant changes from the previous tracing. The patient was able to be ambulatory two days later, and continued to improve. On the sixteenth hospital day an operation was performed.

Differential Diagnosis

Dr. Walter S. Kerr, Jr.*: Dr. Gibbons, may we see the films?

Dr. John F. Gibbons: There are two sets of chest films, the first made on admission and the others three days later. Initially, there was enlargement of the heart primarily in the region of the left ventricle, some evidence of engorgement of the main pulmonary vascular channels and a picture quite consistent with a moderate amount of cardiac decompensation. In three days the congestion has cleared pretty well although the heart is still enlarged and the aorta is quite tortuous and sclerotic. The intravenous pyelogram discloses that the right kidney functions well, and its collecting system looks normal. On the left no intravenous dye is seen up to forty minutes after injection, when the examination was terminated. In the films of the abdomen taken after this examination there is a soft-tissue density in the left side of the abdomen adjacent to the midlumbar spine that one can see through the gas-filled stomach. The left kidney, however, cannot be clearly outlined — it cannot be outlined completely on any of the films. The barium-enema study shows that the colon is not displaced by anything in the lower abdomen; there are a few diverticula in the sigmoid.

Dr. Kerr: Do you see any evidence of an aneurysm either of the aorta or of the renal arteries?

Dr. Gibbons: I see nothing that makes me suspect an aneurysmal mass. The retrograde pyelogram gives us more information. There is hydronephrosis on the left side, with dilatation of the renal pelvis and calyceal structures, and the axis of the kidney is changed so that it lies apparently with its medial portion closer than usual to the spine (Fig. 1). The soft-tissue mass that I pointed out before, which one sees through the gas-filled stomach, seems to be in the position that the upper pole of the kidney would normally occupy, and there is a second density that is made up primarily of the dilated renal pelvis and the ureter, which now has to take a course at right angles to its lower portion because of the rotation of the kidneys in the vertical axis and also the rotation in the other axis.

Dr. Kerr: What axis is that?

Dr. Gibbons: There is a rotation outward of the upper pole and also a rotation internally on the vertical axis so that the renal pelvis comes to lie in a plane toward the middle of the abdomen more than the right renal pelvis.

Dr. Kerr: Do you think that the pelvis is pushed toward the posterior wall or anteriorly?

Dr. Gibbons: I should think it is pushed anteriorly. The calyxes of the upper pole do not seem to be filled out, and there seems to be a flat indentation on the collecting system in this area; an oblique film shows for the first time what may be the upper pole of the kidney. There is a shadow that is roughly ovoid whose upper pole is at least 6 cm. above the filled part of the collecting system.

Dr. Kerr: What is the relation of that to the mass?

Dr. Gibbons: As far as I can tell, the abnormal density in the region of the left kidney is connected to the kidney. I cannot separate the soft-tissue mass from the mass that I think is kidney shadow.

Dr. Kerr: Where is this fleck of calcium?

Dr. Gibbons: This calcification may be in the upper pole of the kidney, or it could be in the wall of the aorta.

Dr. Kerr: This is a left oblique view?

Dr. Gibbons: Yes; the lower ureter is apparently of normal caliber.

Dr. Kerr: This eighty-year-old woman had a perplexing history of hematuria and sudden onset of severe pain in the left flank. I shall start with the state of the heart, about which I have been straightened out by my medical friends. Obviously, from the clinical picture of dilated neck veins, large liver and ankle edema and the x-ray examination of the chest, she had some failure both of the right and of the left side of the heart.

The second subject to deal with is the alkalosis; the carbon dioxide was 36 milliequiv. per liter, and it is difficult for me to explain this, unless the patient vomited more than was stated in the protocol.

The absence of the cervix I can quickly dismiss. She received irradiation to the uterus nineteen years before admission; no other mention was made of that.

The urinary infection was apparently limited to the bladder, for the urine collected from the bladder grew *Esch. coli* on culture, and that from the left kidney was sterile. In view of this negative culture infection of the left kidney as a cause of the elevated white-cell count can be ruled out.

*Assistant urologist, Massachusetts General Hospital.

The cause of the flank pain and hematuria in a patient with a white-cell count of 22,800, no fever and no chills and a hemoglobin of 12 gm. per 100 cc. is certainly perplexing. The nausea and vomiting are not unusual in cases of ureteral obstruction, and I assume that they were due to the difficulty in the left kidney rather than to an upset in the gastrointestinal tract itself. Although the protocol does not state whether blood was ever seen coming from the left ureter on cystoscopic examination I shall assume, since the pain in the left flank and the gross hematuria started at the same time, that the bleeding was from the left kidney rather than from the cystitis or from the other kidney.

The x-ray films are not as helpful as I had anticipated. From the description in the protocol I had expected to see a greater degree of hydronephrosis than is present. The right kidney appears to be of normal size and therefore was probably doing a normal amount of work. If the left kidney were only a hydronephrotic sac, one would expect to see a hypertrophied right kidney. The causes of hydronephrosis in people of this age can be as varied as those at any other age. One of the commonest causes is obstruction resulting from stones. She did not have stones unless they were uric acid stones that did not show up in the x-ray films. There may have been a congenital defect of the ureteropelvic region. The lower ureter seemed to be normal; therefore, whatever was causing the hydronephrosis was primarily in the region of the ureteropelvic junction. Ordinarily, a congenital defect with hydronephrosis comes to the attention of the patient and the physician long before the age of eighty. This is not always so, however, for I have operated on a seventy-four-year-old woman and found 400 cc. of urine in the kidney pelvis because of a congenital abnormality. Another possible cause of hydronephrosis is a tumor of the kidney pelvis. Several years ago I operated on a seventy-eight-year-old woman with a squamous-cell carcinoma of the ureteropelvic junction that had resulted in a hydronephrotic sac containing 1000 cc. Another possibility is extrinsic pressure either from enlarged metastatic lymph nodes or from some pelvic organ such as the ovary or uterus.

Certainly, the most likely cause of hematuria is a tumor, either a hypernephroma or possibly a papillary or epidermoid tumor of the kidney pelvis. All these tumors can metastasize to lymph nodes in the region of the kidney pelvis and can cause pressure defects in the pelvis and may explain the suggestion of encroachment on the renal pelvis mentioned in the protocol.

Before seeing these films I was convinced that the patient had a hemorrhage from the cortex of the kidney that had bled into and broken through the capsule of the kidney, resulting in bleeding into the perirenal fat. That would explain the high white-cell count without fever, the rotation of the kidney and the sudden onset of severe pain, which is often accompanied by nausea and vomiting. Of course, other retroperitoneal organs or tumors can bleed and give this same picture. The mass in the upper pole of the left kidney as described by Dr. Gibbons was probably a tumor with hemorrhage into the perirenal tissues. I suppose the operation was an exploration of the kidney. I think I should have done an aortogram first.

DR. JOHN A. MALCOLM: On the service we thought that the patient probably had a tumor and was in danger of having another massive hemorrhage. In addition we believed that the attacks of renal colic on the basis of the blood clots were probably a precipitating factor in the anginal attacks and therefore something that should be eliminated. About an aortogram, we thought that if we pushed in a needle we might detach an arteriosclerotic plaque, which might stop at the aortic bifurcation. Thus, we considered this procedure about equal in risk to an exploratory operation. We gave her a long time to recover medically from the congestive heart failure and awaited the word of the medical service before we undertook the operation. She did particularly well.

CLINICAL DIAGNOSIS

Renal tumor.

DR. WALTER S. KERR, JR.'S DIAGNOSIS

Tumor of kidney, with bleeding into perirenal tissue.

ANATOMICAL DIAGNOSIS

Renal-cell carcinoma, lower pole, and cortical cyst, upper pole, left kidney.

PATHOLOGICAL DISCUSSION

DR. DAVID KAHN: The removed kidney was enlarged, weighing 320 gm. The inferior three fourths was replaced by tumor, scattered throughout which there were multiple areas of hemorrhage and necrosis; I think that probably the necrosis was responsible for the raised white-cell count. Microscopical examination showed this to be a renal-cell carcinoma. The tumor had not broken through the capsule, and no definite hydronephrosis could be recognized in the removed kidney. The tumor had not invaded the renal vein, and the portion of the artery accompanying the kidney was normal. Occupying the superior third of the kidney was a large simple cyst, which probably explains the bizarre picture observed on the retrograde pyelogram. When the patient was seen four months after the operation, she was well and without complaints.

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QUEEN'S OF CANADA

Two years ago note was made in the *Journal* of the hundredth anniversary of the Faculty of Medicine of Laval University under its present organization, for in 1852, when Laval received its royal charter, it also acquired the four-year-old Quebec School of Medicine. This year, with the centennial observance of the founding of Queen's Medical College in Kingston, the fourth of Canada's fifteen medical schools has reached the century mark.

Some of the story of Queen's is given in the special centenary issue of the *Canadian Medical Association Journal* for March, an issue contributed largely by the members of Queen's Medical Faculty and containing a leading guest editorial by Austin Smith, editor of the *Journal of the American Medical Association* and one of Queen's distinguished graduates.

On October 16, 1841,—quite unconscious of the fact that on this date, five years later, the use of ether would be first publicly demonstrated at the Massachusetts General Hospital,—the youthful Victoria, beginning the fifth year of her reign, issued the charter that established Queen's University at Kingston. Kingston was then little more than a military outpost in the colony of Upper Canada, but it was situated at the strategic point on Lake Ontario where the St. Lawrence River begins its outflow and the Rideau Canal system joins the two. This, the St. Lawrence seaway project of that day, was designed by Wellington to afford communication with Montreal via Byetown (now Ottawa). The present university campus was purchased in 1853, and early in the following year plans were made for the opening of a faculty of medicine in the fall.

The officers of instruction in the Faculty of Medicine of Queen's now consist of 38 full-time and 138 part-time teachers of medicine and the medical sciences. Clinical instruction is given in the hospitals of Kingston and Ottawa. A six-year course leads to the degree of M.D., C.M., and graduate courses lead to the degrees of M.Sc. (Med.), and Ph.D., and certification in the various specialties. Some 400 matriculants from Canada and other parts of the Commonwealth and the United States comprise the student body.

The governments of both the Dominion of Canada and the Province of Ontario contribute to the support of Queen's University, and in 1953 the 2000 graduates of the Faculty of Medicine donated approximately $75,000 to their own school. Casual students of heraldry will be interested in the reproduction on the cover of the special Queen's issue of the *Canadian Medical Association Journal* of the Armorial Ensigns of the University, granted on August 31, 1953, by the Kings of Arms of Queen Elizabeth the Second.

The *New England Journal of Medicine* takes the occasion of extending its own felicitations to the Faculty of Medicine of Queen's University in this memorable year of its history.

RELATIVE SIGNIFICANCE

MEDICAL science is committed to accurate measurements and the reporting of these measurements in figures that are meaningful. However, the unit that is frequently used for reporting various clinical observations is not necessarily the one most significant. It behooves every scientist to appreciate the accuracy of his measurements and to record the results in appropriate figures.

How many physicians believe that the blood pressure recorded as 120 systolic, 75 diastolic, is accurate to the last millimeter? It has been demonstrated that the recording of the blood pressure within 5 mm. is as accurate as one can hope for. When one considers the fluctuations of blood pressure from one minute to the next it is frequently impossible to obtain two readings that agree within 10 mm. of mercury. Would it not, therefore, be more reasonable to report blood pressure in *centimeters* of mercury? The physician can be quite certain of the pressure in centimeters, and such reporting would eliminate guesswork regarding the last millimeter. The reporting of blood pressure in centimeters of mercury has been in practice in other countries—France, Greece and Mexico—for many years.

The recording of the blood pressure in centimeters would also help to de-emphasize minor pressure changes, particularly in the hypertensive patient, since a change of 2.5 cm. does not sound nearly so impressive as a change of 25 mm. The use of smaller and more significant figures would also have a less damaging effect on the patient's morale, when he learns that his blood pressure is 20 rather than 200.

Another measurement that is frequently carried out clinically and reported in millimeters is the venous pressure. It should be evident to any person who takes venous pressure that the correction factor alone of 50 mm. of water, more or less, is necessary for the estimation of the distance from the angle of Louis to the right atrium. It would therefore be much more appropriate to report such measurements in centimeters rather than millimeters. The same statement could apply equally well to cerebrospinal-fluid pressure.

A plea, therefore, is made for the reporting of observations in units about which the physician can be certain. The folly of attempting to quantitate observations that are not subject to accurate measurement is quite obvious.

DEATH IN THE ICEBOX

ONLY recently has there come full realization of the hazards of the discarded refrigerator, which, always a menace, has become one of increasing importance ever since the electric refrigerator began to replace the old-fashioned icebox. The very nature of its function—to provide a hermetically sealed and insulated cabinet— and the ingenious absolutism of its one-way latch make it as perfect a deathtrap as if it had been designed for the purpose.

In very recent years, convinced at last of society's responsibility in the matter, laws are being considered and passed requiring the removal of latches or doors from unused or discarded refrigerators before they are left where the adventurous young can enter them. To facilitate such protective legislation the Refrigeration Service Engineers Society has drafted the following model law, here reprinted from *Safety Education Data Sheet No. 62*, issued by the National Safety Council:

> Anyone who abandons, discards, stores or keeps in any place accessible to children, or who, as the owner, lessee, or manager, permits to remain on his premises under his control, a refrigerator, icebox, freezer cabinet or similar container, of a capacity of one and one-half cubic feet or more, which is no longer used for refrigeration purposes, without the attached doors, hinges, lids or latches being removed, is guilty of a misdemeanor and shall be punished by fine of not more than Fifty ($50) Dollars, or by imprisonment for not more than thirty (30) days or both.

The question remains, however, whether a punitive law can take the place of educational enlightenment.

The same data sheet supplies certain interesting and arresting statistics on this totally unnecessary menace, and gives other information of value. For the years prior to 1948 this information is incomplete; apparently, the problem began to assume major proportions after the war when the electric-refrigerator industry swung back into full production and the number of discarded boxes sharply increased.

According to statistics now available, in the six years from 1948 to 1953, inclusive, 1 to 5 children in each of nearly 50 incidents have been trapped in ancient but air-tight refrigerators. Fifty-nine boys and 20 girls, ranging in age from two to twelve years, have thus had their lives literally snuffed out from lack of oxygen. It is significant that the number of fatalities in 1953 was double that in 1952, with the average number of deaths per incident increasing. Thus in 1953, 12 children died in 4 such accidents, in 1 case 5 children from a single family being the victims. The magnitude of the problem is further indicated by the estimate of more than 50,000,000 refrigerators and other air-tight cabinets in use at the present time and their replacement at the rate of 2,000,000 to 3,000,000 a year.

It all adds up to the fact that "there are both *more and more inviting* discarded refrigerators and freezers for children to crawl into today" and the responsibility for taking the spring out of the trap belongs to the community and the individuals who comprise it. This means seeing that the latch-stop at least and preferably the entire door is removed from any refrigerator large enough for a small child to crawl into, before it is stored or abandoned. Other more or less effective methods of rendering the trap relatively harmless are removing the door gasket and drilling holes into the interior, storing the refrigerator with the door against the wall and wiring the door shut or padlocking it.

BLOOD SALVAGE

ATTENTION is directed to a notice published in the Massachusetts Medical Society column of the current issue of the *Journal* regarding the salvage of serum albumin and plasma from the unused quantities of human blood that have been collected primarily for transfusion purposes. Obviously, more blood must be collected and on hand at the various blood banks in the Commonwealth than there may be immediate use for at any time, which means always a constant stream of outdated blood that must be removed from the stock piles available for whole-blood transfusion.

This outdated blood amounts to some 15 per cent of the total 150,000 to 155,000 pints collected, which can and should be but unfortunately is not regularly returned to the Red Cross Center for processing into stable plasma fractions, or saved for plasma extraction for fluid therapy. The annual waste actually is estimated to reach the appalling quantity of 10,000 to 15,000 pints.

Conscious of the situation and of the possibility of correcting it, as has been done during the last five years in Michigan, a plasma-salvage subcommittee of the Committee for Supervision of the Red Cross Blood Program has been organized to develop a program for collecting all unused blood and directing it into the useful channels available. Blood voluntarily shed is a symbol of sacrifice; its waste is a symbol of indifference to sacrifice.

The attention of readers is directed to a continuation, in to-day's Journal, of Dr. Haskell's views on the vital endowment of nerves.

Boston M. & S. J., *July 12, 1854*

MASSACHUSETTS MEDICAL SOCIETY

HUMAN SERUM ALBUMIN AND PLASMA SALVAGE

The following statement on outdated blood is presented for the information of fellows of the Society:

About 140,000 blood transfusions are given annually in Massachusetts hospitals, according to statistics gathered recently by the Massachusetts Medical Society's Committee for Supervision of the Red Cross Blood Program. This large amount of whole blood is obtained through activities of hospital blood banks and from the Red Cross by volunteer donations, each source providing about half the total. The Committee has also ascertained that the number of bloods collected by the hospital and Red Cross blood banks exceed the number of transfusions by 15 per cent. An excess is inevitable in any sound blood program, but the fate of the excess blood after outdating as useful whole blood has had the concerted attention of the Committee. Some of the outdated blood is returned to the Red Cross Center, which provides for further processing into stable plasma fractions. In some blood banks plasma is drawn from outdated bloods and used as such in fluid therapy. Most of the outdated blood, however, seems to be wasted—an annual estimated waste of 10,000 to 15,000 pints of human blood.

A plasma-salvage subcommittee (Dr. William Freeman, chairman, and Drs. Huston J. Banton and Johannes Ipsen, Jr., members) has therefore been established and is now embarking on a program to collect the scattered pints of unused blood from all over the State, so that it may be processed into serum albumin and other useful plasma fractions.

Outdated whole blood from blood supplied by the Red Cross should, as hitherto, be returned to the Red Cross Center. The labeling of the bottles will leave no doubt of the origin of the blood. Outdated blood from hospital blood banks should be sent directly to the Division of Biologic Laboratories, 375 South Street, Forest Hills, Boston 30, Massachusetts, preferably as single or pooled units of plasma.

Serum albumin will be returned to hospitals in proportion to the amount of plasma or outdated blood that is received by the Institute. The plasma from 10 pints of blood will yield 100 cc. of 25 per cent low-salt albumin, the commercial price of which is about $60.

Albumin can replace plasma in most patients with low serum protein, and is superior to plasma in patients with hypoalbuminemia. It is free of the virus of serum hepatitis, the hazard of which is a serious obstacle to the use of plasma. Albumin is also free of iso-agglutinins so that there is no problem of incompatibility. It is therefore useful in the emergency treatment of oligemic shock.

In the use of human serum albumin it should be noted that a 100-cc. vial represents the osmotic protein equivalent of approximately 500 cc., or 2 units, of human plasma. Dilution at least fivefold in saline solution or glucose is necessary before intravenous administration because of its powerful osmotic strength.

A similar plasma-salvage program has worked satisfactorily for the past five years in Michigan, where the State Laboratories in Lansing annually collect plasma from some 15,000 pints of outdated blood and return albumin to 70 hospital blood banks. Massachusetts is the only other state in the nation that is fortunate enough to possess a state-owned blood fractionation laboratory that can offer free return of albumin to hospitals. The hospital blood banks and physicians in Massachusetts should utilize these facilities to eliminate the waste of outdated human blood and to make available an efficient and costly therapeutic agent in the form of human serum albumin.

MARK FALCON LESSES, M.D.
Chairman
Committee for Supervision of the Red Cross Blood Program

NOTICES

SOCIETY MEETINGS AND CONFERENCES

JULY 12–AUGUST 23. Consultation Clinics for Crippled Children in Massachusetts. Page 1054, issue of June 17.

JULY 22 and 23. International College of Surgeons. Regional Meeting. Page 828, issue of November 12.

JULY 23–29. International Cancer Congress. Page 914, issue of November 26.

JULY 26–31. International Congress of Gynecology and Obstetrics. Page 400, issue of March 4.

AUGUST 1–7. Pan-American Congress of Pediatrics. Page 850, issue of May 13.

AUGUST 17–20. Argentine Congress of Thoracic Surgery. Page 708, issue of April 22.

SEPTEMBER 6–10. International Poliomyelitis Congress. Page 399, issue of March 4.

SEPTEMBER 6–11. University of Illinois College of Medicine. Annual Assembly in Otolaryngology. Page 1092, issue of June 24.

SEPTEMBER 7–10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.

SEPTEMBER 12–15. Second International Congress of Cardiology. Washington, D. C.

SEPTEMBER 13–15. American Association of Blood Banks. Page 968, issue of June 3.

SEPTEMBER 16–18. American Heart Association. Annual Scientific Sessions. Washington, D. C.

SEPTEMBER 22. New England Pediatric Society. Page 968, issue of June 3.

OCTOBER 1 and DECEMBER 3, 1954; FEBRUARY 4 and APRIL 1, 1955. New England Society of Anesthesiologists. Page 1054, issue of June 17.

OCTOBER 7 and 8. Pan-Pacific Surgical Association. Page 1092, issue of June 24.

(Notices concluded on page xxiii)